CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

Moderated Poster Discussion: The Role of Glucose Testing and Variability *(Posters: 861-P to 868-P), see page 21.*

861-P

"Intra-day" and "Day-to-Day" Glucose Variability Both Increase Oxidative Stress Determined by d-ROMs in Type 2 Diabetes: A Cross-Sectional Study

MAKOTO OHARA, TOMOYASU FUKUI, MOTOSHI OUCHI, KENTARO WATANABE, TATSUYA SUZUKI, TAKESHI YAMAMOTO, TOSHIYUKI HAYASHI, KENZO OBA, TSUTOMU HIRANO, *Tokyo, Japan, Tochigi, Japan, Yamagata, Japan, Ibaraki City, Japan*

Aims: Previous clinical studies have found associations between oxidative stress and intra-day glucose variability, but none have reported data linking oxidative stress with glucose variability from day to day. We decided to examine how oxidative stress correlates with both intra-day and day-to-day glucose variability in type 2 diabetes.

Methods: The study was designed as a cross-sectional analysis of 68 patients with type 2 diabetes (studied 2012-2015) who underwent 72 hours of continuous glucose monitoring (CGM). The glucose variability, mean glucose level (MGL), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), and total area under the curve of postprandial plasma glucose (AUC_{PP}) were measured on days 2 and 3. Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) were measured before breakfast on day 1. As a marker of oxidative stress, the plasma total oxidant capacity against N, N-diethylparaphenylendiamine was measured by the d-ROMs test on day 1.

Results: The 68 participants had a mean age of 63.2±12.6 years, with a mean disease duration of 12.9±10.4 years and HbA1c of 8.14±1.64%. MGL, HbA1c, MAGE, MODD and AUC_{PP} exhibited significant correlations with d-ROMs, but not with FPG, in univariate analysis. MGL, HbA1c, MAGE, MODD and AUC_{PP} remained significantly related to d-ROMs after adjustment for clinical factors (sex, age, duration of diabetes, smoking habit, insulin use, statin use, angiotensin II receptor blocker use, BMI, LDL-C, HDL-C, TG, eGFR, Systolic Blood Pressure), whereas FPG did not. In multivariate regression analyses, MAGE and MODD were correlated with d-ROMs after adjustment for markers of diabetic control. MAGE was also significantly correlated with MODD.

Conclusions: The present study is the first to demonstrate that oxidative stress is associated with both intra-day and day-to-day glucose variability in patients with type 2 diabetes.

862-P

WITHDRAWN

863-P

First Results from a National Registry on the Effect of Real-Time Continuous Monitoring in Poorly Controlled Patients with Type 1 Diabetes

HAROLD W. DE VALK, BIANCA SILVIUS, TRACING- STUDY GROUP, *Utrecht, Netherlands*

Real-time continuous glucose monitoring (rtCGM) is effective and safe in improving glycemic control in randomized trials in patients with type 1 diabetes mellitus (DM1). Less is known in general clinical use. We conduct an ongoing national voluntary registry in the Netherlands on use, efficacy and safety of rtCGM in DM1 ("regisTRAtion of ContINuous Glucose monitoring" (TRACING)), operated by an independent, publically-funded hospital consortium (BIDON). rtCGM is reimbursed for adults with HbA1c ≥ 64 mmol/mol, pregnant women and children on insulin pump. Here we report on poorly controlled adults starting with rtCGM.

59 of 94 hospitals are actively participating; 951 adults have been included; 471 patients were reported as "poorly controlled adults;" 109 were pregnant, 321 "other reasons" (most notably hypoglycemia), 50 were unclassified. Demographics, medical history and outcomes are recorded locally and collected in the coordinating center (UMC Utrecht). Of the 471 poorly controlled patients, 146 were recruited at start of rtCGM.

Of the 146 patients: mean age: 40.8±11.5 years, female: 65.1%, duration of disease: 21.1±11.7 years, DM1: 95.9%, insulin pump 92.5%. Symptomatic neuropathy was present in 17.4%, retinopathy in 31.9%, nephropathy in 5.6%, autonomic neuropathy in 8.9% and macro-angiopathy in 3.4%. Eighty-two patients had a follow-up of 6 months. After 6 months, mean HbA1c had fallen from 67.7±8.6 to 61.3±9.0 mmol/mol (p<0.001); mean difference 6.4±9.3 mmol/mol. Fifty-six patients had actually an HbA1c ≥64 mmol/mol at baseline. Mean HbA1c in this group fell from 71.8±7.2 to 63.6±8.9 mmol/mol (p<0.001); mean difference 8.2±9.7 mmol/mol.

The results of this multi-center registration suggest that implementation of rtCGM in real life setting is successful with a considerable improvement in glycemic control in those patients with poor control. It also stresses the risk of misclassification in data-input from participating centers.

864-P

Failure of Fasting Blood Glucose Screening to Detect All Persons with Diabetes or Prediabetes

JAMES H. ANDERSON, STEVEN C. KENDALL, ROCCO BRUNELLE, CORAL S. MAY, SUSAN H. MILLER, MICHAEL MCENTEE, LEE B. SPRINGER, *Indianapolis, IN, Mansfield, TX, Carmel, IN*

As increasing rates and complications of diabetes consume an ever-expanding portion of health care costs, earlier diagnosis of type 2 diabetes mellitus (T2DM) becomes increasingly important. Screening for T2DM at community and ADA health fairs and large wellness programs has varied over time, but now focuses on questionnaires or fasting blood glucose (FBG) measurements.

To examine the efficacy of using FBG as a screening tool, data was analyzed from 22,498 subjects, in a de-identified Health and Wellness Screening Database, who had no prior diagnosis of glycemic disorders and had both FBG and hemoglobin A1c (A1c) measurements. Subjects were 64% female, 82% Caucasian, 6% Hispanic, 5% African American, and 4% Asian. They ranged in age from 18 to 84, had an average BMI of 29, an average A1c of 5.5%, and an average FBG of 93 mg/dL. The correlation between FBG and A1c was 0.45. Of the demographic variables examined, increasing age was the factor most closely associated with elevated A1c.

Interestingly, there were 297 subjects with an A1c ≥6.5% but an FBG <126mg/dL, identifying a need for additional evaluation for potential T2DM. Using stricter criteria, 135 of those subjects had an A1c ≥6.5% but an FBG <100mg/dL. Importantly, 4400 subjects had an A1c ≥5.7% but <6.5% with a FBG of <100 mg/dL, suggesting a need for further evaluation for pre diabetes, a condition where lifestyle management may have an effect in preventing or delaying complications.

Conversely, 228 subjects had an A1c <6.5% and an FBG >126mg/dL (98 of whom had an A1c <5.7% and an FBG >126mg/dL) suggesting they were not truly fasting, but resulting in a need for additional costs for retesting and evaluation.

This study suggests that almost 4700 subjects (20% of the group) with potential diabetes or prediabetes would have failed to be detected in a screening program that used only a FBG with the standard cut point of 126 mg/dL. Consideration should be given to the approval and widespread use of HbA1c testing for the screening of diabetes and prediabetes.

865-P

Sleep Apnea in Patients with Type 1 Diabetes: Relationship with Glucose Variability and Autonomic Neuropathy

LAURENT MEYER, CLÉMENCE CANEL, JEAN-PIERRE LE FLOCH, PARISA ASSEMI, ANNE ELISABETH PERRIN, ELISABETH WURTZ, PHILIPPE BALTZINGER, CÉLINE LUTZ, ALEXANDRE LECLERCQ, CARMEN LAMENDI, ROMAIN KESSLER, LAURENCE KESSLER, *Strasbourg, France, Villecresnes, France, Saverne, France, Mulhouse, France*

Some studies report a high prevalence of obstructive sleep apnea (OSA) in patients with type 1 diabetes but the links between OSA and type 1 diabetes are poorly studied. OSA defined by an apnea-hypopnea index (AHI) of >10/h, was investigated among 140 patients with type 1 diabetes by polysomnography (n=59) or ventilatory polygraphy (n=81). A continuous subcutaneous glucose monitoring (CGM Dexcom) was performed simultaneously in 54 patients and glucose profiles were compared during sleeping and waking periods in patients with and without OSA over 24 hours. Autonomic neuropathy was assessed in a subgroup of 16 patients by measuring hands and feet conductance (SUDOSCAN test) which provides an evaluation of sweat gland function.

The average age of the population was 49.9±12.9 years, BMI 25.9±4.4 kg/m², duration of diabetes 27.0±14.5 years, and HbA1c 7.8±1.2%. OSA was diagnosed in 35.7% of patients. Patients with OSA were mainly men: 66% ($p<0.05$), older: 54.4±11.7 years ($p<0.05$), with a longer duration of diabetes: 34.5±13.0 years ($p<0.05$) and a higher BMI: 27.2±4.4 kg/m² ($p<0.05$). HbA1c was similar in both groups: 7.7±1.0% vs. 7.8±1.3%. CGM data were compared in patients with (n=13) and without OSA (n=41). Glucose variability indices (SD, VC, MAG, hypoglycemia) were increased during the waking period in patients with OSA ($p<0.001$). The time spent in hypoglycemia tended to increase in the OSA group during sleep (3.3% vs. 1.2%) and to decrease during the waking period (2.2% vs. 4.8%). There was a positive correlation between AHI and time spent in hypoglycemia ($p<0.05$) and a negative correlation between AHI and hands and feet conductance ($p<0.001$), suggesting that patients with OSA have more frequent autonomic neuropathy.

Conclusion: Type 1 diabetic patients with OSA have an increased glucose variability during waking period and a trend to nocturnal hypoglycemia. This increase in OSA prevalence and glucose variability in type 1 diabetes may be linked to autonomic neuropathy.

Supported By: IP-Santé; Johnson & Johnson; Impeto Medical

866-P

Assessment of Glucose Variability by Professional Flash Glucose Monitoring across Therapy Groups for Type 2 Diabetes

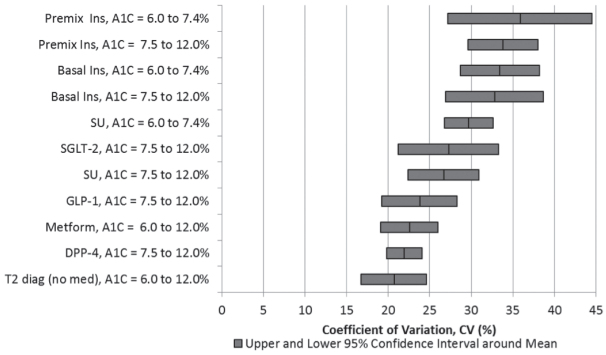
KURT MIDYETT, DEANNA CHEUNG, JEFFREY R. UNGER, EUGENE E. WRIGHT, TIMOTHY D. DANIEL, DAVIDA F. KRUGER, ROBERT R. HENRY, *Kansas City, MO, Long Beach, CA, Chino, CA, Fayetteville, NC, Pearland, TX, Detroit, MI, San Diego, CA*

Glucose variability was assessed in adults on type 2 therapies using novel investigational sensor glucose monitoring (FreeStyle Libre Pro™, Abbott Diabetes Care) for up to 14 days. Patients had A1c of 6.0 to 12.0% for groups managed with education (n=11), Metformin (n=12), sulfonylurea (n= 25), basal insulin (n= 21), and premixed insulin (n=18), but restricted to an elevated A1c (7.5 to 12.0%) for DPP-4 (n=6), SGLT2 (n=4), and GLP-1 (n=8).

There were no serious device-related adverse events during the study, and glucose values were obtained for a mean of 296 (SD = 79, median = 333) hours per subject. The lowest glucose coefficient of variation (CV) was found for education therapy, followed by DPP-4 and Metformin. Inspection of the 95% confidence intervals found these groups did not overlap with SU (A1c 6.4-7.4%), basal (A1c 6.0-12.0%) and premixed insulin (A1c 6.0-12.0%) groups. CV was the most sensitive measure of glucose variability to therapy regimen, describing 37% (r=0.61) of the variation.

This study found increased glucose variability across all T2 diabetes therapy groups compared to reports in healthy subjects (by 128 to 284%). There were detectable differences in variability among the therapy groups, and those with the most elevated variability approach that reported in T1 diabetes.

Figure.



Supported By: Abbott Diabetes Care

867-P

Human Factors and Home Use Study of the Vigilant Diabetes Management Application

DANIEL CHERNAVVSKY, ERIK OTTO, CHRISTOPHER DING, CHRISTIAN WAKEMAN, MARY C. OLIVERI, STACEY M. ANDERSON, *Charlottesville, VA*

The Vigilant™ Diabetes Management Application uses advanced pattern recognition technology to notify patients about risk of severe lows in the next 24 hours, and also alerts to upcoming daily patterns of highs, lows, variability and gaps in testing. A human factors and home use study has been completed to assess whether subjects with diabetes and their caregivers can understand feedback received about their blood glucose patterns and whether the decisions made in response to device feedback are in accordance with the intended use.

Vigilant was evaluated in 15 diabetes clinicians and 46 T1DM or T2DM patients using MDI or CSII (16 adolescents, 15 adults, 15 elderly). The application was evaluated for ease of use and comprehension, and subjects completed frequent and risk-related tasks in an office environment. In addition, the 46 patients used Vigilant at home for 30 days and completed similar ease-of use and comprehension surveys at study end. Comparisons of 30 day clinical measures of blood glucose (BG) control were also made at study completion vs. baseline.

Human factors and ease of use performance criteria were met across all subjects, as well as within pre-defined clinician and patient subgroups. On a scale of 1 (Poor) to 5 (Excellent), average ratings for pattern comprehension, ease of use and overall were 4.7, 4.5 and 4.0 respectively. Clinical measures of BG control including average BG, ADRR, LBGI, HBGI, and % in range, were all improved, and notably, the rates of biochemical severe hypoglycemia (SMBG <40 mg/dL) and extreme highs (SMBG > 400 mg/dL) were reduced by 50.9% and 20.4% respectively in the Vigilant home use period vs. baseline.

Vigilant demonstrated favorable human factors and usability ratings across all intended users. Clinical data analyses suggest that Vigilant may reduce dangerous glucose excursions without compromising mean glucose levels. Future studies will elucidate if this effect can be reproduced in a large randomized trial or within specific at-risk patient groups.

868-P

Using Novel Flash Glucose-Sensing Technology Reduces Hypoglycemia in Individuals with Type 1 Diabetes

JAN BOLINDER, RAMIRO ANTUNA, NEL GEELHOED-DUIJVESTIJN, STEPHAN MATTHAEI, RAIMUND WEITGASSER, *Stockholm, Sweden, Madrid, Spain, The Hague, Netherlands, Quakenbrück, Germany, Salzburg, Austria*

Hypoglycemia is a barrier to intensive insulin therapy and influences quality of life. We assessed the impact of new sensor technology on hypoglycemia compared to conventional self-monitoring of blood glucose (SMBG). 241 subjects with well controlled type 1 diabetes (T1DM), [HbA1c 6.74±0.56% (50.1±6.1 mmol/mol), age 43.7±13.9 years and average duration of diabetes 22±12 years (mean±SD)] were recruited into a 6 month European study (23 sites). The control group (n=121) used capillary glucose-testing (FreeStyle Lite™) and the intervention group (n=120) used sensor glucose data (FreeStyle Libre™ Flash Glucose Monitoring System) for self-management. At 6 months, the time in hypoglycemia <70 mg/dL (primary outcome) was significantly reduced by 38.0% [mean difference -1.24±0.239 hours per day (mean±SE); $p<0.0001$]. Time <40 mg/dL was reduced by 65.3%; ($p=0.0003$). Reductions were evident both during day and night with nocturnal hypogly-

For author disclosure information, see page A696.

cemia <70 mg/dL reduced by 39.8%; (p<0.0001). Time in hyperglycemia (>240 mg/dL) was significantly reduced by -0.37±0.163 hours per day (p=0.0247) and time in range (70-180 mg/dL) was significantly increased by 1.0±0.30 hours per day (p=0.0006). There were no differences in mean glucose or HbA1c. Using FreeStyle Libre™, scanning frequency averaged 15.1 per day, whereas SMBG tests dropped from a median of 5.4 (baseline) to 0.1 per day. In the control group, SMBG remained unchanged at 5.6 per day. Ten subjects experienced 13 device related AEs, e.g., allergy, itching, rash, erythema and edema (6 severe, 4 moderate, 3 mild), with 5 subjects withdrawing due to the event. Treatment satisfaction (DTSQ, DQoL), perception of hyperglycemia (DTSQ) and quality of life (total score for DQoL) were significantly improved. It is concluded that well controlled T1DM subjects using novel flash glucose monitoring technology reduced time in hypoglycemia without deterioration of HbA1c and reported improvements in quality of life.

Supported By: Abbott

Moderated Poster Discussion: Glucose Sensing Helps *(Posters: 869-P to 876-P), see page 20.*

869-P

Continuous Glucose Monitoring Improved Glycemic Control in Patients with Type 1 Diabetes in a 52-Week Period, either with Insulin Pump Therapy or with a Basal-Bolus Insulin Regimen

JAN SOUPAL, LENKA PETRUŽELKOVÁ, MILAN FLEKAC, JAN SKRHA, JR., JAN SKRHA, MARTIN PRAZNY, *Prague, Czech Republic*

To compare different treatment strategies for patients with type 1 diabetes in a 12-month prospective study. 54 subjects with comparable baseline parameters were divided into 3 groups. The first group of 19 patients started to use real-time continuous glucose monitoring (RT-CGM) for at least 70% of the time. In this first group, 11 patients started to use insulin pump and sensors (SAP) and the other 8 continued with multiple daily injection (MDI + RT-CGM). The second group of 18 patients initiated insulin pump (CSII) therapy alone and the third group of 17 subjects continued just on MDI. At the baseline, all patients were monitored by blinded CGM and underwent structured training. In addition, the groups without RT-CGM had a week of blinded CGM every 3 months. The main endpoints were reduction of A1c, glycemic variability (GV) expressed as standard deviation (SD) and incidence of hypoglycemia (% of time below 3.9 mmol/L). After a year, patients on RT-CGM had significantly lower A1c (67±11 vs. 55±11 mmol/mol; p<0.0001), and both subgroups, with SAP and with MDI, showed comparable improvement in A1c. CSII therapy without RT-CGM also led to A1c reduction (68±9 vs. 63±8 mmol/mol; p<0.05), while no significant A1c decrease was seen in the group just on MDI (67±9 vs. 65±10 mmol/mol; NS). Importantly, any treatment using RT-CGM was superior to CSII therapy alone (A1c: 55±11 vs. 63±8 mmol/mol; p<0.05). Compared to the baseline, GV was lower both in the RT-CGM group (SD: 4.1±0.7 vs. 3.0±0.5; p<0.0001) and in patients with CSII alone (SD: 3.8±0.7 vs. 3.4±0.6; p<0.01). Reduction of time spent in hypoglycemia was observed only in patients with RT-CGM (8±4 vs. 6±3%; p<0.01). RT-CGM provided similar A1c reduction in patients using either MDI or CSII therapy. This improvement was superior to insulin pump therapy alone. The combination of RT-CGM and MDI can be a suitable alternative to the SAP system for some patients.

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870-P

Standardized Evaluation of Three Continuous Glucose Monitoring Systems under Routine Clinical Conditions

JULIA K. MADER, MARTIN HAJNSEK, FELIX ABERER, MARKUS RUMPLER, SABINE ZENZ, ADELHEID PUFFING, HESHAM EL-SAYED, THOMAS AUGUSTIN, FRANK SINNER, THOMAS R. PIEBER, *Graz, Austria*

Continuous glucose monitoring (CGM) has become an essential tool in diabetes management. In order to use CGM for treatment decisions, CGM systems have to be reliable over a wide range of glycemia as well as in situations with rapidly changing glucose levels. In this monocentric study we evaluated the performance of 3 commercially available CGM systems (Abbott Libre, Dexcom G4 Platinum, Medtronic Enlite) in 12 type 1 diabetic subjects (age 33 ± 11 y, 42% women, BMI 22.5 ± 2.4 kg/m^2, diabetes duration 17 ± 12 y, HbA1c 7.6 ± 1.1%) over a period of 12 hours. Routine clinical conditions were mimicked by meal and exercise tests. The sensors were inserted 24 hours prior to the test in parallel and were calibrated according to manufacturers' instructions. Reference plasma glucose samples were taken every 5 minutes throughout the study and measured with Super GL analyzer. Glucose measurement accuracy was determined for each CGM system according to ISO 15197: 2013 guideline (±15%; ±15 mg/dL for glucose <100 mg/dL). The systems fulfilled these criteria as follows: 73.1% (Abbott), 56.1% (Dexcom) and 52.0% (Medtronic). Additional accuracy metrics are indicated in Table 1. In summary, the Abbott sensor showed superior performance based on all accuracy metrics applied in this study. All sensors were less accurate during hypoglycemia. Future CGM generations need to be improved regarding accuracy in the low glucose range.

Table 1. Continuous Glucose Monitor Performance.

	Abbott (n=462)	Dexcom (n=540)	Medtronic (n=502)
Overall Mean Absolute Relative Difference (MARD)	13.22 ± 10.87	16.75 ± 12.31	21.36 ± 17.60
MARD <70 mg/dL	14.61 ± 10.34	23.77 ± 15.66	26.86 ± 20.02
MARD 70-≤180 mg/dL	13.68 ± 11.53	16.34 ± 11.64	20.94 ± 15.34
MARD >180 mg/dL	10.09 ± 7.93	11.56 ± 7.24	17.15 ± 21.85
Parkes Error Grid Zone A (%)	85.71	83.52	71.12
Parkes Error Grid Zone B (%)	14.29	15.74	27.49
Parkes Error Grid Zone C (%)	0	0.74	1.39

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871-P

Hypoglycemia Reduction in Sensor-Augmented Pump Therapy (SAP) with Predictive Low Glucose Management (SmartGuard™) in Children with Type 1 Diabetes

OLGA KORDONOURI, TORBEN BIESTER, THOMAS DANNE, MARTIN HOLDER, KERSTIN REMUS, TANJA WADIEN, KIENINGER-BAUM DOROTHEE, ANDREAS THOMAS, *Hannover, Germany, Stuttgart, Germany, Mainz, Germany, Meerbusch, Germany*

The "MiniMed® 640G" system offers the SmartGuard™ (SG) algorithm. Based on sensor glucose values it predicts when a patient approaches low glucose levels 30 minutes in advance leading to insulin suspension and resumption when glucose levels recover. In a prospective pediatric study, we investigated the effect of SG under real-life conditions. 18 patients with type 1 diabetes (age 11.6±5.1 (range: 3-18) years, diabetes duration 7.5±4.2 years, CSII experience 6.4±4.4 years, A1c 7.4±0.7%) were studied during 3 subsequent time periods: CSII with MM640G only (4 weeks), then SAP without SG (2 weeks), followed by SAP with SG (6 weeks). The primary objective was to assess the frequency and intensity of hypoglycemia (AUC and time < 70 mg/dL) using the SG feature. Provisional data showed 3.15±1.03 "interruptions before low"/day, a total pump stoppage time of 155±47 min/d and pump stoppage time/event of 60.5±2.5 min. The average nadir glucose during the shutdown was 77.9 mg/dL (10% <55 mg/dL). The average suspension glucose level was 108.6±3.6mg/dL, while the mean resumption glucose was 106.4±2.4 mg/dL. Comparing SAP with and without SG, hypoglycemia events and intensity decreased significantly by using SG (Table). The present study provides evidence for reducing the risk for hypoglycemia with SG without compromising the safety of CSII therapy in pediatric patients.

Table.

Parameter of Hypoglycemia	SAP without SG	SAP with SG	p (t-test)
Excursions/day < 70 mg/dL	1.02±0.52	0.72±0.36	0.038
Excursions/day ≤ 40 mg/dL	0.20±0.22	0.10±0.10	0.034
AUC/Tag < 70 mg/dl (mg/dL*day)	0.576±0.73	0.38±0.24	0.029
Time/day < 70 mg/dL (min)	72.9±55.9	30.6±21.5	0.007
Intensity (AUC x time) < 70 mg/dL	91.5±130.5	17.6±20.6	0.022

Supported By: Medtronic Deutschland

872-P

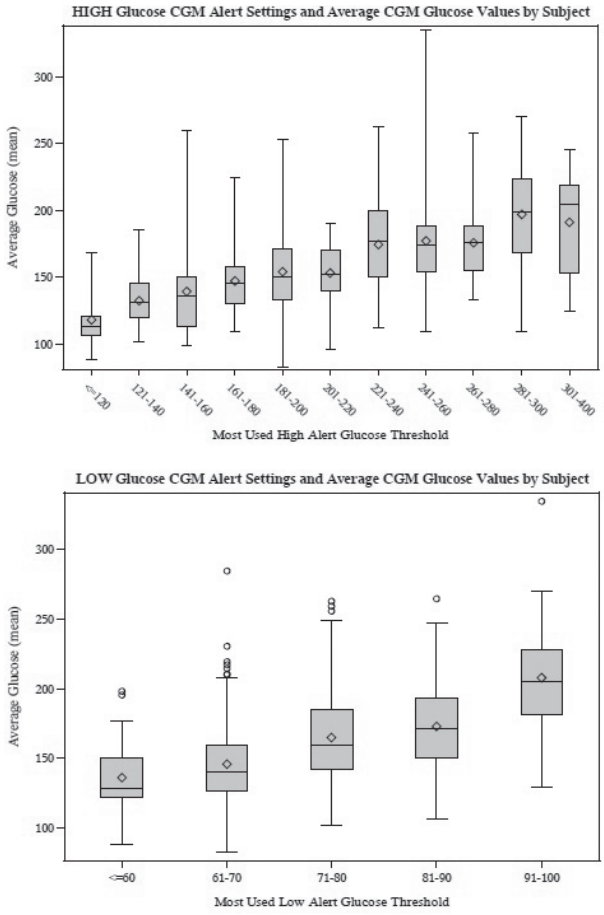
Patient Data from RT-CGM Suggests Use of Threshold Alerts Impacts Glycemic Control

KATHERINE NAKAMURA, TOMAS WALKER, ANDY BALO, *San Diego, CA*

The aim of this retrospective data analyses was to evaluate the impacts of CGM threshold alerts in glycemic control from patient's real world CGM data. The real-time CGM data were collected from patient voluntarily uploads for technical support. We calculated glycemic variability measurements, such as average and standard deviation (SD) of CGM glucose. we also identified the most frequent (Mode) low glucose alert level (LGL) and high glucose alert level (HGL) chosen by the patients on their CGM devices, as well as the average daily screen views and their demographic information. 48% of patients

(N=550) were male, and their average age was 38 ± 23 years-old, ranging from 2 to 85. There were 17.5 M records of data and the average time of CGM use was 78 ± 72 days. 92% of users set their electable alerts; 77% of users chosen a LGL at 80 mg/dL or lower; and 79% of users used a HGL at 180 mg/dL or higher. On average, they checked the CGM screen 29 ±18 times daily. The data reveal that glucose average and SD correlated with their most frequent LGL and HGL levels (r=0.478, 0.490, 0.299, 0.411; respectively, all p<.0001). When users set their glucose alert levels lower, their average and variation of the CGM glucose decreased significantly. Patients' age, daily screen view showed an inverse relationship with lower correlation coefficients (r= -0.347, -0.099, -0.347, -0.210; respectively).

Figure 1. Average Glucose Decreased with Lower CGM Alert Levels.



873-P

Pilot Study of Tidepool's Blip Application for Data Visualization in Type 1 Diabetes (T1D)

JENISE C. WONG, AARON B. NEINSTEIN, HOWARD LOOK, BRANDON ARBITER, NORA CHOKR, CASSIE ROSS, SALEH ADI, *San Francisco, CA, Palo Alto, CA*

Frequent adjustment of insulin regimens is important for good glycemic control in T1D, which requires routine review of blood glucose (BG) data, carbohydrates, and insulin doses. Although both health care providers (HCPs) and patients can review data from insulin pumps and continuous glucose monitoring (CGM) to adjust insulin regimens, a small proportion of patients review data regularly, in part because downloading data from devices and/or using device software is difficult. We have created the Tidepool platform, which collects and hosts T1D data, and a software application, Blip, which displays data in a uniform, device-agnostic manner. In this pilot study, patients (n=39) and caregivers of children (n=32) with T1D who had used a pump ± CGM for >1 year, completed a survey on data review, were given access to Blip for 3 months, and provided feedback on Blip. At baseline, nearly all participants (95.8%) felt that it was important for patients to know how to interpret BG data, and most felt that both the HCP and patient should review data (71.8%), look for patterns (80.3%), and make changes to the insulin plan (76.1%), rather than the HCP or patient alone. However, despite valuing shared responsibility, at baseline, 42% of participants never downloaded pump data at home, and only 8.5% did this at least once per month. At the end of the study, 73% downloaded data at least once, and 37% downloaded at least once per month. Regarding Blip, participants commented positively about the central repository of data, the intuitive design, and the user interface. Users liked that pump and CGM data could be reviewed together and were interested in continuing to use Blip after the study concluded. Suggestions included providing tools for understanding and interpreting BG patterns, a wireless uploading process, and access on mobile devices. Future studies will test new versions of Blip with an updated data acquisition process, and will focus on HCP use, longer duration of use, and effect of use on clinical and behavioral outcomes.

Supported By: National Institutes of Health

874-P

Clinical Use of CGM Results in Reduced Frequency of BGM

TOMAS C. WALKER, DAVID A. PRICE, KERI J. LEONE, *San Diego, CA*

Persons who use Continuous Glucose Monitoring (CGM) have been instructed to base clinical decisions on Blood Glucose Monitoring (BGM) results. However, CGM technologies have shown significant improvements in performance and error reduction, and are approaching SMBG accuracy. A CGM device recently received CE Mark approval for diabetes management decisions without requiring confirmatory BGM.

No published clinical studies (RCT) have evaluated outcomes when CGM is used as a replacement for BGM. If CGM users perform less BGM, it suggests clinical decisions are based on CGM. This analysis looked at studies to determine the impact of CGM use on BGM frequency.

Eleven CGM outcome studies reported since 2008 were reviewed for reported changes in BGM frequency. Six trials did not report frequency of BGM use while 5 trials reported quantified reductions (Table 1).

Data from the T1 Diabetes Exchange, demonstrates that patients across a range of ages are reducing BGM frequency after initiating CGM therapies and CGM outcome trials that quantify SMBG frequency demonstrate improved glucose control and decreased dependence on BGM. Improving CGM technologies should engender greater trust and result in greater reliance on CGM-based decisions.

Table 1.

Reference	N	Duration of CGM use	SMBG Reduction from Baseline	Comments
Direct Net Study Group, 2008	N=27	3 mos.	>40% Reduction (p = 0.16) NS	Compared run-in to completion
Riveline et al. 2012	N=178	12 mos	>50% Reduction (p < 0.0001)	Subjects were trained in aggressive DM self-management
Battelino et al. 2012	N=153	6 mos crossover	0.6 tests/day (p < 0.0001)	Removal of CGM resulted in loss of metabolic benefit
Bergenstal et al. 2013	N=247	3 mos	0.6 tests/day (**ns)	Identical reported reduction in SMBG in both SAP and LGS
2015 JP New et al.	N=145	100 days	>50% Reduction (p < 0.0001)	Reduction noted in both CGM groups

875-P

Optical Glucose Sensor for Single-Port Glucose Monitoring

MARTIN HAJNSEK, MARKUS RUMPLER, JULIA K. MADER, THOMAS PIEBER, *Graz, Austria*

We developed a new technology which combines continuous glucose monitoring and insulin infusion into one single-port system for simultaneous glucose measurement and insulin delivery to improve glycemic control in type 1 diabetes patients.

Contrary to currently used artificial pancreas systems with two separate devices, namely a glucose monitor and an insulin pump, the SPIDIMAN single-port system integrates two luminescence-based sensors as thin coatings directly on the cannula of an insulin infusion set. One sensor uses glucose oxidase to enzymatically detect oxygen consumption for glucose concentration measurements. The second sensor is used to measure tissue oxygen levels to compensate for oxygen variations over time. The read-out device is placed on the patch of the insulin infusion set and the sensor signals are read-out transcutaneously via contactless near-infrared radiation. In preclinical in-vivo experiments in pigs we tested whether insulin infusion had any effect on glucose measurement when performed at the same site. We also evaluated sensor performance in a clinical trial including 12 diabetes patients.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

No influence of insulin infusion on glucose measurements was observed in the preclinical tests. Glucose sensors with a basal insulin infusion rate of 1.2 U/h had a median ARE of 21.6% ± 5.7%, sensors with an infusion of 12 µl/h physiological NaCl solution had a median ARE of 18.1% ± 5.8% and sensors with no infusion had a median ARE of 19.2% ± 7.9%. Sensor glucose values were calculated with a retrospective calibration using a linear regression. Mean ARE values achieved in the clinical trial ranged from 12% to 36% considering variations caused by in-house sensor production.

Our results demonstrate that glucose measurement at the site of insulin delivery is feasible. Our single-port system successfully combines continuous glucose monitoring and insulin infusion into one device and has therefore great potential to become the central element of an artificial pancreas.

Supported By: European Union (305343)

876-P

WITHDRAWN

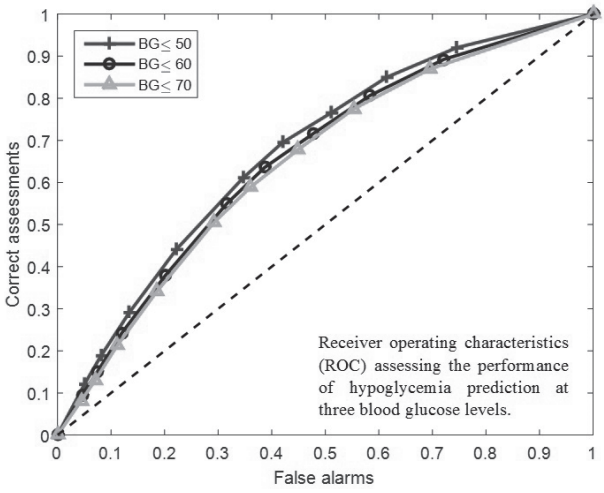
877-P

Decision Support via Real-Time Tracking of Risk for Hypoglycemia in Diabetes

CHIARA FABRIS, MARC D. BRETON, BORIS P. KOVATCHEV, *Charlottesville, VA*

For the majority of patients, episodic self-monitoring (SMBG) is the primary information source driving treatment decisions. As a result, critical parameters such as ongoing risk for hypoglycemia may remain unrecognized. Here we introduce a method that uses fasting SMBG data to track risk for hypoglycemia continually. Training data (169 type 1 diabetes patients; 28215 SMBGs of which 4416 fasting collected over 1 month) were used to develop a method for dynamical tracking of risk for hypoglycemia from SMBG. The method was fixed in the training data and was then tested in an independent cohort of 114 subjects (188390 SMBGs, 33006 fasting over 10 months). In the test data, the probability for impeding hypoglycemia below 70, 60, 50 mg/dl within 24 hours from a warning was 55%, 40%, and 21%, with odds ratios of this prediction of 1.7, 2.0, and 2.6, respectively. The nadir of blood glucose (BG) following a warning was 67 mg/dl compared to 86 mg/dl when there was no warning for hypoglycemia, p<0.001. The ROC curves for predicting hypoglycemia below 70, 60, 50 mg/dl indicated reliable prediction of these events (Figure). Real-time tracking of the risk for hypoglycemia is possible, even with sparse (fasting only) SMBG data. When the method indicates risk, the odds for an event are highest (2.6-fold) for the lowest BGs <50 mg/dl. We conclude that estimated risk for hypoglycemia can be continually available in support of optimal diabetes decisions.

Figure.



Supported By: Sanofi

878-P

Fewer Days of High and Low Blood Glucose Readings with Novel Technology

JANELLE DOWNING, JENNIFER SCHNEIDER, *Mountain View, CA*

Given the growing prevalence and increasing costs of managing diabetes, there is a pressing need for self-insured employers, at-risk providers, and payers to find novel ways to address this dual concern.

This study measures blood glucose control for people using a cellular-enabled blood glucose meter with real-time, personalized, context-aware, actionable recommendations provided by Livongo Health.

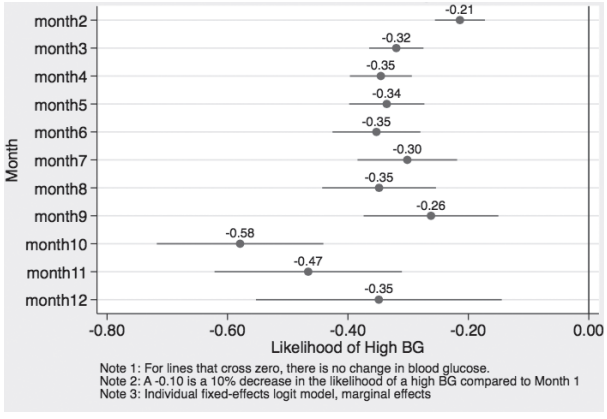
We studied 3,355 members across 34 firms from the time of initiation with the program through October 15, 2015. We used an individual fixed-effects logit model to look at the odds of having a daily blood glucose reading >180 mg/dL or <80 mg/dL in subsequent months compared with month one as baseline.

For the 3,355 members studied, 55% were female, 86% had type 2 diabetes, 58% did not report insulin use, and 65% were between ages 45-65 years. There was a statistically significant reduction in the odds ratio of having a day with a blood glucose reading >180 mg/dL or <80 mg/dL in all eleven subsequent months compared to baseline.

This work suggests that a cellular-enabled blood glucose device with personalized recommendations reduces the likelihood of having both high blood glucose and low blood glucose readings sustained over eleven months.

Opportunities for further exploration include broadening the definitions of high and low blood glucose readings, extending the measured time period, and directly measuring financial costs.

Figure. Likehood of BG Above 180 Compared to Month 1.



879-P

Accuracy of a Fourth-Generation Glucose Sensor at Different Anatomical Locations

BRUCE W. BODE, RON BRAZG, MARK CHRISTIANSEN, TIMOTHY S. BAILEY, SATISH GARG, ROBERT SLOVER, JOHN B. WELSH, FRANCINE R. KAUFMAN, *Atlanta, GA, Renton, WA, Walnut Creek, CA, Escondido, CA, Denver, CO, Aurora, CO, Northridge, CA*

Accuracy of a fourth-generation subcutaneous glucose sensor was evaluated over the course of 7 days for sensors inserted into either the upper arm or abdomen. After a 7-day run-in phase, each subject wore abdominal sensors attached to transmitters specific for data storage and processing on either the MiniMed 640G insulin pump or a smartphone app, and an additional sensor on the upper arm attached to a non-transmitting recorder. Subjects underwent 12-hour in-clinic visits on study days 1, 3, and 7 for frequent sample testing (FST) of plasma glucose with a reference instrument (YSI). Sensor glucose (SG) values were compared with YSI glucose values for accuracy analyses. Eighty-nine subjects were enrolled and 82 completed the study. A total of 10,526 paired SG-YSI values were available from arm sensors and 23,709 from abdomen sensors. The overall mean absolute relative difference (MARD) ±SD for arm sensors was 9.1 ± 8.29% and for abdomen sensors was 10.5 ±10.01%. Mean and median MARD values for each FST and each anatomical location are shown in the Table. SG data from either arm- or abdomen-placed sensors compared favorably to YSI values throughout the sensors' 7 day functional life. Arm-placed sensors were more accurate than abdomen-placed sensors. Results support use of this sensor for standalone, open-loop, and closed-loop systems.

Table. Fourth-Generation Glucose Sensor Accuracy by Anatomical Location.

		N	MARD, % Mean ± SD	MARD, % Median
Day 1	Arm	3390	10.8 ± 9.46	8.2
	Abdomen	8307	12.7 ± 11.10	9.8
Day 3	Arm	4243	8.1 ± 7.17	6.5
	Abdomen	8827	8.8 ± 8.05	6.7
Day 7	Arm	2893	8.5 ± 8.06	6.4
	Abdomen	6575	9.8 ± 10.38	7.1

Supported By: Medtronic

880-P

Safety and Accuracy Evaluation of San MediTech's Real-Time Continuous Glucose Monitoring (RT-CGM) Device

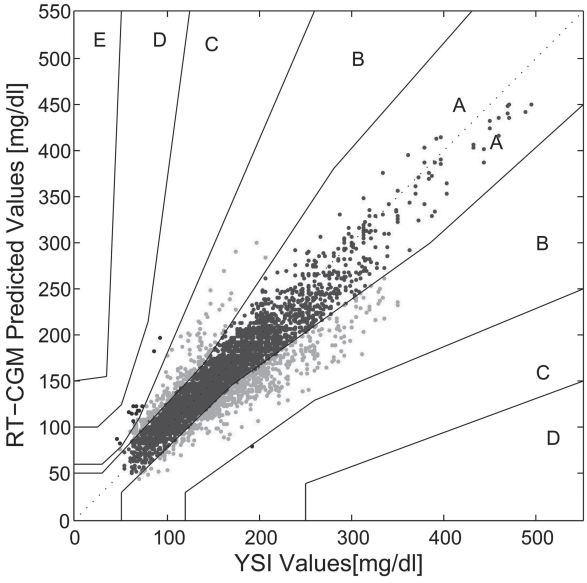
DAN WANG, HUASHI ZHANG, *Beijing, China*

The purpose of this study is to evaluate the safety and the accuracy of the San MediTech (SMT)'s Real-Time Continuous Glucose Monitoring (RT-CGM) device through the comparison with the capillary and the venous blood glucose reference values.

Seventy-three subjects were enrolled in the study with Peking University First Hospital and The Second Xiangya Hospital of Central South University from July to November, 2015. Each subject wore two SMT's RT-CGM devices on their right and left upper arms for consecutive 4 days. Each day 7 capillary glucose values were measured with the glucose meter (Accu-Chek, Germany) as the reference glucose values. On Day 3 and the last day of the study, 32 venous blood glucose references (YSI 2300 STAT, U.S.) were measured for each subject every 15 min during a 4-hour period.

The total numbers of the capillary and the venous blood glucose reference values are 6944 and 4518 pairs respectively. All subjects completed the study and no safety adverse event was observed. The MARD (mean absolute relative difference) values of SMT's RT-CGM device compared with YSI and SMBG are 12.1% and 13.6% respectively. The percentages of sensor value fell in plus minus 20% of comparative glucose reading are 83.4% and 77.4%, respectively to YSI and SMBG. The Consensus Error Grid Analysis Plot of the SMT's RT-CGM values vs. YSI is shown in the below Figure. 99.7% fell within Zones A and B.

Figure. Consensus Error Grid Analysis.



881-P

In Vivo Study of Acetaminophen Interference on the Continuous Glucose Monitoring Using the Direct Electron Transfer-type Sensor

SHINJIRO SEKIMOTO, *Kyoto, Japan*

Objective: We have been developing a novel CGM sensor utilizing glucose dehydrogenase (GDH) complex from Burkholderia cepacia. This enzyme is unique as it does not require oxygen or additional electron acceptors (mediators) for glucose monitoring, but has the ability to transfer electrons directly to an electrode, thereby realizes "Direct Electron Transfer (DiET) " principle for glucose monitoring. Thanks to this feature, sensors employ this principle realize in the reduction of the working potential of the electrode, which is beneficial in avoiding the effect of electroactive ingredients. The aim of this study is to evaluate the effect of acetaminophen on the CGM sensor signals, which employs DiET principle at the lower working potential. We also report the CGM performance of this sensor *in vivo* human trial for 14 days.

Method: A CGM sensor employs DiET principle (DiET CGM sensor) consisting of three electrodes was used. Sensor working potential was +0.15V (vs. Ag/AgCl). The *in vivo* study was performed to evaluate CGM performance of this sensor for 14 days. The subject was dosed with a total dosage of acetaminophen of 0.9g. The concentration of plasma acetaminophen, plasma glucose, capillary blood glucose were determined during CGM testing. All tests were carried out after obtaining informed consent.

Result: When acetaminophen was taken, the plasma acetaminophen concentration peaked at 28.7μg/mL after around 30 minutes. However, no acetaminophen influence was observed for the DiET CGM sensor glucose value measured at 0.15V, compared with the plasma and capillary blood glucose concentration. The MARD between the CGM and the BGM readings for 14 days was 9.3%.

Conclusion: The effect of acetaminophen with the possible *in vivo* level concentration is negligible in the glucose values obtained from the DiET CGM sensor. The sensor showed stable CGM response for more than 14 days with single digit MARD (9.3%) under the operational condition employing low potential.

882-P

WITHDRAWN

For author disclosure information, see page A696.

883-P

OneTouch Verio Performance at Extremes of Glucose and Hematocrit

STEVEN J. SETFORD, STEPHEN MACKINTOSH, STUART PHILLIPS, HILARY CAMERON, LESLEY MILLER, MIKE GRADY, *Inverness, United Kingdom, Wayne, PA*

The performance of One Touch Verio blood glucose test strips was assessed at extremes of hematocrit and glucose using clinic derived data. Since product launch in 2010, manufactured batches of Verio have been routinely sampled and system accuracy assessed on diabetes subjects in clinic, yielding a dataset of 63,023 points, with accompanying reference and hematocrit values. A histogram of patient hematocrit values was constructed by inverse empirical fit and subject data occupying the highest and lowest 1st percentile hematocrit ranges calculated:

Lowest 1st percentile range: 22.5-30.7%
Highest 1st percentile range: 50-59.6%

Data points within these ranges were assessed against the glucose ranges as set-out in the ISO 15197:2013 system accuracy specification (≥95% of values to be within 15mg/dL or 15% of reference, at <100 mg/dL or ≥100mg/dL glucose respectively). Results are shown below at low (>50-80 mg/dL) and high (>400 mg/dL) glucose, with >95% of all values meeting specification at the hematocrit extremes. When all glucose levels were combined, 99.08% and 97.27% of strips tested met the ISO system accuracy criterion at the lower and upper hematocrit percentiles respectively.

Table.

Glucose Range (mg/dL)	Accurate (n)	Total (n)	Accurate (%)
Lowest 1st percentile range: 22.5-30.7%			
>50-80	30	31	96.77
>400+	21	21	100.00
Highest 1st percentile range: 50-59.6%			
>50-80	47	49	95.92
>400+	91	92	98.91

884-P

Continuous Measurement of Glucose at the Site of Insulin Delivery: Challenges and Solutions

W.K. WARD, SHEILA BENWARE, CHAD KNUTSEN, MATTHEW BREEN, KRISTIN MORRIS, JOSEPH KOWALSKI, GABRIEL HEINRICH, ROBERT S. CARGILL, *Portland, OR*

Combining continuous glucose monitoring (CGM) and insulin delivery in a single device would reduce device burden in T1D. We examined mechanisms by which the preservatives in insulin (phenol, *m*-cresol, "phenolics") impair CGM at the site of subcutaneous (SC) insulin delivery. To identify mechanisms of interference, we compared 2 CGM devices developed at PDT: (1) Pt-based sensor, polarized at +600 mV ("conventional"), and (2) Au-based sensor with osmium-based redox mediator, polarized at +180 mV ("mediated"). We also developed miniaturized aluminosilicate filters located within the insulin path. We found 4 types of interferences due to phenolics: (1) A rapid current rise simulating hyperglycemia ("early rise"); (2) an exponential current decline from electropolymerization ("decay"); (3) a stable step decline; and (4) a permanent decline in sensitivity ("poisoning"). Some conventional sensors had an inner membrane of electrodeposited organic polymer ("EOP"). Both sensor types were exposed to phenolics, 1.5 mg/ml. Conventional sensors without EOP showed a large early rise, a marked decay and poisoning. Conventional sensors with EOP showed a slow early rise, minimal decay and no poisoning. Mediated sensors had no early rise, no decay, and no poisoning, but had a step decline. Aluminosilicate filters removed 85-95% of the phenolics from insulin formulations. In Yucatan pigs, we also studied SC sensing catheters into which conventional sensing elements had been integrated. Of 26 data sets, 15 showed signal artifact after bolus insulin. Lack of artifact was associated with smaller insulin dose and location of indicating electrodes farther away from insulin delivery site. In summary, sensor design factors that reduce the interfering effects of insulin preservatives at the site of insulin delivery include: (1) an inner EOP membrane; (2) a redox mediator; (3) an aluminosilicate filter; and (4) location of electrodes farther away from the insulin source.

Supported By: National Institutes of Health; The Leona M. and Harry B. Helmsley Charitable Trust

885-P

Severity of Sepsis Associated with Hyperglycemia and Glycemic Variability in Nondiabetic Subjects

LUKANA PREECHASUK, NANTAWAN IPICHART, NATTAKARN SUWANSAKSRI, NATTACHET PLENGVIDHYA, SATHIT VANNASAENG, CHAIRAT PERMPIKUL, APIRADEE SRIWIJITKAMOL, *Bangkok, Thailand*

Hyperglycemia is associated with mortality in sepsis. Retrospective study showed the glucose variability (GV) related with mortality in these groups, but there are limited data of GV in sepsis. The aims of this study were to compare the mean glucose (MG) and GV between sepsis and healthy subjects and to determine the relation between MG, GV and the sepsis severity.

Sepsis patients without history of DM and A1c < 6.5% were enrolled. All subjects had 72-h continuous glucose monitor; CGM within 12 hours after admission. 72-h CGM was applied to healthy subjects to serve as a control. Glucose levels obtained from CGM at 24-h and 72-h were used to calculate $MG_{(24h, 72h)}$ and GV including SD ($SD_{24h, 72h}$) and mean amplitude of glycemic excursion ($MAGE_{24h, 72h}$). We used SOFA and APACHE II to assess the sepsis severity.

30 sepsis and 10 healthy subjects were enrolled. Mean age of sepsis group was higher than healthy control. Sepsis had higher MG and GV than control. The mortality rate of sepsis in this study was 13%. We compared the MG and GV between survivor and non-survivor, patients with SOFA <9 and ≥9 and patients with APACHE <25 and ≥25. Table 1 showed the difference in MG and GV between groups.

In conclusion, nondiabetes sepsis had high MG and GV. MG was strongly associated with the sepsis severity whereas GV were not consistently associated with the sepsis severity. Thus the association between GV and sepsis severity need more study.

Table 1.

		Survivor N=26	Non survivor N=4	SOFA<9 N=24	SOFA ≥9 N=6	APACHE<25 N=24	APACHE2≥5 N=6
Mean	24-hr	143±29	199±13*	139±27	195±17*	140±28	195±17*
	72-hr	140±31	178±9	140±31	178±9	136±29	177±18
SD	24-hr	19 (5, 58)	32 (28, 36)*	19 (5, 58)	32 (16, 55)*	19 (7, 58)	30 (5, 55)
	72-hr	21 (9, 61)	32 (29, 33)	21 (9, 61)	33 (17, 42)	22 (9, 61)	28 (18, 40)
MAGE	24-hr	55 (16,179)	94 (76,113)*	54 (16,179)	94 (58,153)*	56 (21,180)	80 (16,153)
	72-hr	65 (26,177)	105 (90,125)	65 (26,177)	105 (53,128)	65 (26,177)	90 (51,114)

*=P<0.05.

886-P

A Bolus Advisor System for the Management of Insulin Therapy in Type 1 Diabetes

ANNA RITA MAURIZI, NACIU ANDA, ROSSELLA DEL TORO, ANGELO LAURIA PANTANO, ELVIRA FIORITI, SILVIA MANFRINI, PAOLO POZZILLI, *Rome, Italy*

Diet, physical activity and proper dosage of insulin play a key role in the management of insulin therapy in type 1 diabetes (T1D) patients on multiple daily injections (MDI). Thus, to obtain optimal glycaemic control, adjustments of insulin dose at meal times must be made by taking into account several parameters as blood glucose levels, the insulin/carbohydrate ratio, the carbohydrate intake at each meal. A bolus advisor system (Accu-Chek®

Aviva Connect) developed for the establishment of the insulin dose to be administer, takes into account all above parameters. Aim of this randomised trial was to evaluate the efficacy of a bolus advisor system on glycaemic control as assessed by HbA1c and patients compliance to Self-Monitoring of Blood Glucose (SMBG), through the use of a telemedicine system. 25 T1D patients were enrolled in the study. HbA1c and patients compliance, assessed as average number of daily measurements and as total measurements, were evaluated at entry into the trial and at 3 and 6 months follow-up. As secondary end-points the number of hypoglycaemic events and the total results above target range were evaluated. Paired t test (two tailed) and analysis of variance were used to evaluate differences in HbA1c at different time points. HbA1c at entry was 7.36% ±0.93 (SD) in patients using this bolus advisor system with bolus calculator and data transmission by App on a Smartphone activated and 7.6% ± 0.62 (SD) in the control group with bolus advisor turned off and on standard education for insulin management (p:NS). After follow-up there was a tendency for an improvement in HbA1c levels in the bolus advisor system treated group vs. control group (7.27% ±0.76% ± vs. 7.86% ± 1.5%, respectively). An improvement in compliance to SMBG in the bolus advisor system treated group compared to control subject was observed. In conclusion, this bolus advisor system is a friendly wirelessly meter that helps to improve glycaemic control with the achievement of glycemic targets and the improvement of patients compliance to SMBG.

887-P

Accuracy of Four Systems for Self-Monitoring of Blood Glucose in the Hands of Patients and Professionals

ULRIKE KAMECKE, ANNETTE BAUMSTARK, NINA JENDRIKE, STEFAN PLEUS, CORNELIA HAUG, GUIDO FRECKMANN, *Ulm, Germany*

According to ISO 15197:2013 section 8, systems for self-monitoring of blood glucose (SMBG) have to fulfill the same accuracy limits in the hands of patients and professionals. In both cases, 95% of results have to be found within the accuracy limits (±15 mg/dl with regard to comparison results at glucose concentrations <100 mg/dl and ±15% ≥100 mg/dl). In this study, the performance of 4 SMBG systems was evaluated with user measurement and additional study personnel measurements.

Measurements with the SMBG systems (Accu-Chek Active [A], Accu-Chek Performa [B], Contour Plus [C] and OneTouch SelectSimple [D]) were performed by 100 diabetic subjects following ISO 15197 after they familiarized with the systems and instructions for use (excerpts translated into German). The measurements were observed by study personnel who documented mistakes and performed measurements with two comparison methods (glucose oxidase and hexokinase), as well as additional SMBG-measurements. Percentages of values within the above mentioned accuracy limits were calculated.

With the glucose oxidase comparison method, the 4 systems had between 72% and 100% of results within the limits when measurements were performed by users and between 65% and 100% when performed by study personnel. When comparing against the hexokinase method, percentages of results within the limits were 55% to 100%, and 49% to 100% respectively. Two systems (systems B, C) fulfilled the criteria regardless of the comparison measurement; one other system could not meet the criteria when user measurements were compared to hexokinase (system A) and one other system did not fulfill the criteria in any of the comparisons (system D).

With 2 of the 4 systems, study personnel achieved better results than the users, and differences between the two comparison methods were mainly seen in the user measurements. Manufacturers should ensure an adequate accuracy in the hands of users, e.g., by reducing potential error sources.

Supported By: Bayer Vital GmbH, Germany

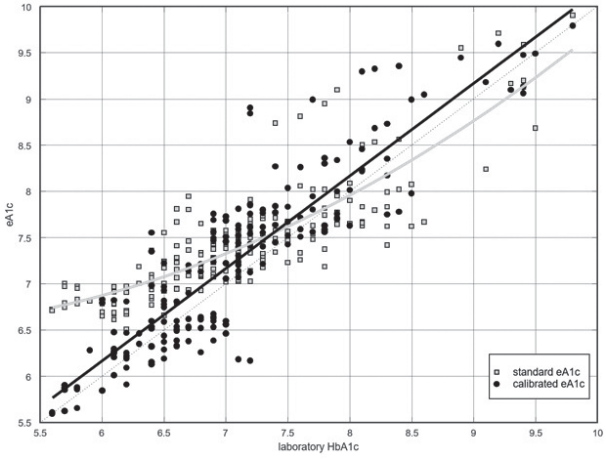
888-P

Decision Support via Dynamic Tracking of HbA1c Using Sparse SMBG Measurements: Effect of Calibration

MARC D. BRETON, JOCHEN SIEBER, GUIDO FRECKMANN, FRANK FLACKE, BORIS P. KOVATCHEV, *Charlottesville, VA, Frankfurt, Germany, Ulm, Germany*

We previously introduced the *eA1c* - a real-time tracker of average glycemia and estimate of HbA1c from infrequent self-monitoring (SMBG) data. Tested in T1DM and T2DM, the eA1c yielded Mean Average Relative Deviations (MARD) between 5% and 8%. We now confirm the accuracy of our method on independent data sets. The study was a 12-week, prospective, national, multicenter, non-controlled, single-arm, open-label study in patients with T1DM and T2DM. SMBG was collected using an iBGStar meter; HbA1c was measured 7 times. A total of 51 patients were enrolled in the study; 50 completed the study, with mean age (± SD) 54.1 ± 12.6 years; 56.9% male 29/51; mean weight 87.4 ± 19.5 kg [52-150 kg]. The eA1c algorithm was applied a posteriori to the SMBG data, using the 1st and 2nd HbA1c as calibration, and others as reference. We contrasted the accuracy of calibrated vs. non-calibrated eA1c. 31862 SMBG records, 166 ± 75mg/dl [40-600], were used in the analysis, corresponding to 348 lab HbA1c, 7.1 ± 0.9% [5.6-9.8]. Non-calibrated eA1c performed as expected: MARD=7.1 ± 5.1%, MAD=0.48 ± 0.32, and correlation ρ=0.85. Calibrated eA1c improved MARD to 4.7 ± 4.1% p<0.001, with MAD=0.33 ± 0.29 and ρ=0.9 (see Figure). With 72% of estimates falling within 6% of lab values (NGSP standard: 92.5%) and estimates within 1% A1c of reference 96.5% of the time (old NGSP: 95%), eA1c showed very robust performance for an SMBG based system.

Figure.



Supported By: Sanofi

889-P

Utility of Ketone Measurement in Determining Resolution of Diabetic Ketoacidosis in a Patient with Mixed Acid-Base Disorders

PREAW HANSEREE, MAXFIELD FLYNN, *Madison, WI*

Ketone measurement is advocated for the diagnosis of diabetic ketoacidosis (DKA), however blood ketones are seldom used for monitoring treatment response and to assess resolution of ketoacidosis. Traditionally, venous pH, bicarbonate, and anion gap have been used to verify the resolution. We present a patient with severe DKA with mixed acid-base disorders due to acute kidney injury (AKI). A 28-year-old female presented to the ED with altered mental status and hypotension. She has no prior history of diabetes, but initial labs revealed arterial gas with a pH of <6.8 and bicarbonate of 3 nmol/L, serum glucose was 661 mg/dL, β-hydroxybutyrate (BOHB) 11.52 mmol/L (normal range 0-0.28), Cr 1.03 mg/dL, HbA1c 17.3%, and drug screening tests were negative. Treatment was started immediately with fluid resuscitation, sodium bicarbonate and IV insulin infusion. She eventually lost her pulse and required 5 minutes of CPR. Her glucose, bicarbonate, and pH gradually improved, but renal function declined. On day 3 of admission, patient remained intubated, her arterial pH was 7.32, bicarbonate 10 mmol/L, Cl 112 mmol/L, anion gap 18 mmol/L, glucose 151 mg/dL, and Cr 2.92 mg/dL. Repeat serum BOHB was 0.11 mmol/L which indicated that DKA resolved. IV insulin was converted to subcutaneous regimen. Patient was weaned off pressors and extubated the next day. Our patient had mixed anion gap and hyperchloremic metabolic acidosis as complications from AKI and high volume of sodium chloride resuscitation. Patients with DKA can develop mixed acid-base disorders, following venous pH and anion gap alone might not be able to determine resolution of DKA. Generally, ketoacidosis should have resolved by 24 hours with appropriate insulin treatment. Serial serum BOHB or capillary blood ketone can be monitored to assess for resolution of DKA, when available. Monitoring blood ketones may allow earlier conversion of IV insulin to subcutaneous insulin and earlier discharge from intensive care unit.

For author disclosure information, see page A696.

890-P

Usability Feedback of the 90-Day Implantable Glucose Sensor in the PRECISE Study

KATHARINE BARNARD, COLLEEN E. MDINGI, PRATIK CHOUDHARY, *Bournemouth, United Kingdom, Germantown, MD, London, United Kingdom*

A new implantable CGM system consisting of a glucose sensor, body-worn smart transmitter and mobile device app was assessed. This analysis reports participant feedback on use of the system continuously for 90 days during the multisite PRECISE study.

A study-specific quantitative and qualitative psychosocial and attitudinal questionnaire was administered to participants with T1 and T2 diabetes. The questionnaire included questions on participants' impression of the features and usability of the CGM system during the study.

Fifty participants across the UK (n=10) and Germany (n=40) completed the questionnaire. Of these, 45 had T1D, 5 had T2D and were equally split between MDI and insulin pump therapy regimen (n=25 each).

The CGM feature with the highest likeability is the mobile device integration (mean 9.6 out of 10) with the ability to display glucose levels and trends, with 72% participants reviewing their glucose display every hour or more frequently than every hour.

The implanted sensor likeability had a mean score of 8.3 (MDI at 8.9 and Pumpers at 7.5). Overall, the implanted glucose sensor was well tolerated with 92% indicating that they did not experience pain or discomfort when using the sensor. 90% indicated they didn't feel the sensor during wear and 86% agreed the sensor insertion was painless. 84% would choose to be inserted again. 90% indicated using the system during the study minimized the burden of diabetes and 88% indicated would like to use the system every day to help manage diabetes more effectively.

Responses correspond with an average improvement in HbA1c from 7.51 to 7.05 (p<0001) over the 90 days use of the CGM.

The CGM sensor was acceptable to participants and using the system was associated with minimized burden of diabetes and improved HbA1c.

891-P

Similar Glucose Control and Hypoglycemia but Reduced Glucose Variability with Glucose Dependent and Independent Therapies in Older Patients with Type 2 Diabetes Mellitus (T2DM)

RICHARD E. PRATLEY, JULIO ROSENSTOCK, SIMON R. HELLER, ALAN SINCLAIR, ROBERT J. HEINE, JACEK KILJANSKI, CYNTHIA S. BRUSKO, RAN DUAN, ANDREAS FESTA, *Orlando, FL, Dallas, TX, Sheffield, United Kingdom, Droitwich, United Kingdom, Indianapolis, IN, Warsaw, Poland, Vienna, Austria*

We compared CGM-assessed glucose profiles (glycemia and glucose variability) of 2 individualized treatment strategies in a subset of moderately ill and/or frail patients ≥65 years with T2DM in IMPERIUM (Individualized treatment approach for older patients in a randomized trial in type 2 diabetes mellitus). Therapies comprised a non-glucose-dependent strategy (NGD, n=21) with a sulfonylurea (SU) and insulin glargine as first injectable and a glucose-dependent strategy (GD, n=26) with a non-SU oral antihyperglycemic medication and a GLP-1 receptor agonist as first injectable. Primary endpoints were duration and % of time spent with blood glucose (BG) ≤70 mg/dL over 24 hours at week 24. Mean ± SD baseline characteristics were similar for GD--NGD: age 69 ± 4--71 ± 5 years, BMI 29.4 ± 4.9--29.2 ± 4.8 kg/m^2, HbA1c 8.5 ± 1.0%--8.3 ± 0.7%, fasting BG 158 ± 38 mg/dL--160 ± 38 mg/dL, and SU use 62%--57%. HbA1c improved in GD vs. NGD by LSM mean -1.2% vs. -1.4%; P<.001 each, with no differences between arms in duration (Table) and % of time spent with BG ≤70 (LSM: 0.44% vs. 1.36%; P=.165) at week 24. Within- and between-day glycemic variability were lower for GD (Table). In conclusion, this CGM sub-study in older patients with T2DM showed lower within- and between-day BG variability for GD but similar HbA1c reductions and hypoglycemia duration for GD and NGD.

Table.

	GD	NGD	GD	NGD		
	Hypoglycemia, Euglycemia, and Hyperglycemia Duration (min) over 24-hr Period					
	N (%, no. pts with an event)		LSM ± SE		Difference (95% CI)	*P* Value
BG ≤70 mg/dL						
Baseline	26 (0.12, 3)	17 (0.29, 5)	9.0 ± 12.2	34.7 ± 15.2	-25.7 (-66.0, 14.5)	.203
Week 24	22 (0.18, 4)	16 (0.38, 6)	6.4 ± 5.7	19.6 ± 6.8	-13.3 (-32.3, 5.8)	.165
BG ≤54 mg/dL						
Baseline	26 (0.04, 1)	17 (0.18, 3)	4.2 ± 10.4	23.1 ± 13.0	-18.9 (-53.3,15.5)	.273
Week 24*	22 (0.05,1)	16 (0.06, 1)	1.2 ± 1.2	0.93 ± 1.5	0.22 (-3.9, 4.3)	.915
BG ≥71 to ≤180 mg/dL						
Baseline	26	17	730.6 ± 86.5	713.4 ± 107.9	17.2 (-268.7, 303.1)	.904
Week 24	22	16	1202.8 ± 47.9	1091.1 ± 56.9	111.7 (-46.0, 269.3)	.158
BG >180 mg/dL						
Baseline	26 (0.89, 23)	17 (0.94, 16)	700.1 ± 90.0	688.9 ± 112.3	11.2 (-286.3, 308.7)	.940
Week 24	22 (0.86, 19)	16 (0.94, 15)	230.7 ± 49.7	326.6 ± 59.0	-96.0 (-259.5, 67.6)	.240
Hypoglycemia Duration (min) During Nocturnal Period						
BG ≤70 mg/dL						
Baseline	26 (0.12, 3)	20 (0.25, 5)	5.3 ± 4.3	13.9 ± 4.9	-8.6 (-22.1, 4.8)	.200
Week 24	22 (0.18, 4)	18 (0.28, 5)	3.7 ± 3.3	11.2 ± 3.7	-7.6 (-18.2, 3.0)	.156
BG ≤54 mg/dL						
Baseline	26 (0.04, 1)	20 (0.15, 3)	1.7 ± 1.6	2.8 ± 1.8	-1.1 (-6.0, 3.9)	.662
Week 24	22 (0.05, 1])	18 (0.06, 1)	0.8 ± 0.8	0.6 ± 0.9	0.18 (-2.3, 2.7)	.885
Glycemic Variability over 24-hr Period						
Within-day BG SD, mg/dL						
Baseline	26	17	42.0 ± 2.5	40.5 ± 3.1	1.5 (-6.6, 9.6)	.710
Week 24	22	16	30.8 ± 2.4	37.7 ± 2.9	-6.9 (-14.9, 1.1)	.090
Within-day BG COV						
Baseline	26	17	22.2 ± 1.6	24.2 ± 1.9	-2.0 (-7.1, 3.2)	.441
Week 24	22	16	21.1 ± 1.2	25.1 ± 1.4	-4.1 (-8.0, -0.08)	.046
Between-day BG COV						
Baseline	24	15	7.3 ± 1.2	8.5 ± 1.6	-1.2 (-5.4, 3.0)	.570
Week 24	19	11	5.4 ± 0.96	9.1 ± 1.3	-3.7 (-7.2, -0.23)	.038

* % of time with BG ≤54 over 24 hours was similar for GD and NGD (LSM: 0.08% vs 0.06%; *P*=0.915)
NOTE: Glycemic variability was calculated using SD and COV for continuous BG readings.
GD=glucose-dependent therapy; NGD=non-glucose–dependent therapy; no=number; pts=patients; LSM=least square mean; CI=confidence interval; BG=blood glucose; SD=standard deviation; COV=coefficient of variance

Supported By: Eli Lilly and Company

892-P

Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial

J. HANS DEVRIES, JORT KROPFF, PRATIK CHOUDHARY, SANKALPA NEUPANE, STEPHEN C. BAIN, CHRISTOPH KAPITZA, THOMAS A. FORST, MANUELA LINK, ANDREW D. DEHENNIS, *Amsterdam, Netherlands, London, United Kingdom, Cambridge, United Kingdom, Swansea, United Kingdom, Neuss, Germany, Mainz, Germany, Ulm, Germany, Germantown, MD*

The accuracy and longevity of a new long term implantable continuous glucose monitoring system (CGM) was investigated over 6 months in the PRECISE study. The Eversense® CGM System (Senseonics Inc, MD) is composed of an implantable, fluorescence-based glucose sensor and a wearable transmitter that wirelessly communicates with a smartphone-based medical app to display glucose results. In this prospective, single-arm investigation 71 adult subjects with T1DM and T2DM were enrolled at 7 clinical sites. Patients used the CGM system at home and in-clinic. During 8 in-clinic visits (8 h-24 h) venous reference glucose measurements were taken (YSI2300 Stat plus) to compare with the glucose measurements from the Eversense CGM system. In parallel to running this study, improvements were made to the glucose calculation algorithm. For the full 180-day enrollment, the median CGM wear duration was found to be 23.5 hours/day with 25th percentile 23.0 hours/day. The real time mean absolute relative difference (MARD) for reference glucose >75mg/dL was 11.1% during the 8 visits over the 180 day period (n=20470, SD 10.1%, 95% CI 10.5%, 11.7%). Mean absolute difference (MAD) for reference glucose ≤75mg/dL was 14.2mg/dl (n=1057, SD 13.5mg/dl, 95% CI 12.1mg/dl, 15.4mg/dl). MARD over the full glycemic range (40-400mg/dL) was 11.6% (n=21527, SD 11.2%, 95% CI 10.9%, 12.2%). Upon applying the algorithm improvements to the PRECISE raw measurement data set, the full scale MARD is decreased to 10.5%. A Kaplan-Meier analysis for survivability of the sensors found 82% and 40% functioning through the 90 day and 180 day in-clinic evaluation sessions, respectively. The Eversense® implantable CGM system was accurate throughout the 6 month, unblinded PRECISE study with an MARD of 11.1% for reference glucose >75mg/dL.

Supported By: Senseonics, Inc.

893-P

Correlation between the Glycemic Variability and the Circadian Blood Pressure Variability in Individuals with Normal Weight and Glucose Tolerance

LIZET ROSALES, LAURA ZUÑIGA, ALEXIS HERNANDEZ, DIEGO HERNANDEZ, ERNESTO CARDONA, CARLOS RAMOS, JULIA RAMOS, MANUEL GONZALEZ, ESPERANZA MARTINEZ, *Guadalajara, Mexico*

Glycemic variability and blood pressure variability have been previously associated with the development and progression of cardiovascular risk. The aim of this study was to evaluate the correlation between the glycemic variability and the circadian blood pressure variability in individuals with normal

weight and glucose tolerance. A cross-sectional study was carried out in 11 subjects of 30 to 40 years, with a body mass index between 18.5-24.9 kg/m^2, with normal glucose tolerance. It was performed an ambulatory continuous glucose monitoring each 5 min for 72 h using an iPro2 (Medtronic, Northridge, CA) and a 24-h ambulatory blood pressure monitoring every 15 min (Microlife WatchBP, Switzerland). Mean amplitude of glycemic excursions (MAGE), area under the curve and mean of daily differences of glucose, as well as, the ratio of blood pressure variability where calculated. Statistical analysis: linear regression and Pearson correlation coefficient. A $p \leq 0.05$ was considered significant. An Ethic Committee approved the protocol and a written informed consent was obtained from all volunteers.MAGE was of 22.79±7.25 mg/dl. The ratio of systolic blood pressure variability was of 7.73±1.60 mmHg and of 10.73±2.10 mmHg to the ratio of diastolic. A significant negative correlation was found between glucose levels and systolic blood pressures (r=-0.598, p<0.05) and diastolic blood pressures (r=-0.691, p<0.05), as well as, for MAGE with the ratio of systolic blood pressure variability (r=-0.726, p<0.05) and the ratio of diastolic (r=-0.924, p<0.05). In conclusion, there was a negative correlation between glucose and blood pressure and between the glycemic variability and the circadian blood pressure variability in subjects with normal weight and glucose tolerance.

894-P

A Novel Index to Identify Steady-State Glucose Infusion Rates during a Clamp

SABINA PAGLIALUNGA, ANGELICA GUERRERO, CLAYTON A. DEHN, *Tempe, AZ*

In clinical research, a hyperinsulinemic-euglycemic (HE) clamp is considered the gold standard to evaluate insulin sensitivity however clamp duration can vary depending on the study. The outcome measure of this method is the glucose infusion rate (GIR). A flat GIR curve suggestive of a steady-state is used to determine insulin sensitivity. Currently, an arbitrary timeframe and coefficient of variance (CV) designates steady-state. Yet, others have shown results may vastly differ depending on where values are extracted from the curve. Here, we applied an empirical formula, originally developed to examine glucose excursions for continual glucose monitoring, to identify GIR steady-state. Healthy adult males (n=6) and females (n=9) were recruited for a 6-hour two-step (10 and 40 mU/m^2*min^{-1}) HE clamp study. Subjects were 28.8±4.2 years old, with a BMI of 22.2±2.2 kg/m^2, and fasting glucose of 85.9±6.8 mg/dL. Steady-state GIR was examined by the novel application of an equation; CONGIR (Continuous Overall Net GIR) calculates the standard deviation of the change in GIR over a given time. A lower CONGIR indicates a flatter segment in the curve. At low insulin infusion, CONGIR was calculated over the 2nd and 3rd hour of the clamp. CONGIR was 0.19 and 0.27, p=NS from 60-120 min and 120-180 min respectively, suggesting both segments were equally flat. Conversely, at higher insulin infusion CONGIR was 0.60 and 0.33, p=0.003 from 240-300 min and 300-360 min respectively, indicating the last hour of the clamp was significantly flatter than the previous. Therefore, a longer protocol yields a more stable GIR at high insulin infusion rates, making these findings pertinent when considering clamp duration. The CONGIR calculation was also more sensitive than % CV in distinguishing flatness. Since HE clamps are widely used in early phase clinical research to evaluate diabetes drug efficacy, a novel measure of GIR flatness is a valuable pharmacodynamics tool for ensuring the integrity of insulin sensitivity determinations.

895-P

The Comparison of Glucose Readings of Continuous Glucose Monitoring and Artificial Pancreas during Glucose Clamp Study

AKIO KURODA, SATOSHI TANIGUCHI, YUKO AKEHI, MOTOYUKI TAMAKI, YINHUA HANAKO OTSUKA, REIKO SUZUKI, MUNEHIDE MATSUHISA, *Tokushima, Japan*

Glucose values of interstitial fluid measured by continuous glucose monitoring (CGM) have time delays compared with plasma glucose (PG) values. Artificial pancreas (STG-55, Nikkiso, Japan) (AP), which measures venous blood glucose directly, and also, has time delay because of the long tubing lines (1.0 m) from sampling vessel to the glucose sensor.

To investigate accuracy and time delay of CGM and AP in comparison with PG values during 2-step glucose clamp study.

Two healthy volunteer and 6 patients with diabetes participated in this study. CGM (Enlite sensor, CA) was attached on the day before the experiment. The calibrations of CGM sensor glucose were done just before and after the clamp study. After an overnight fasting, hyperglycemic (200 mg/dL) clamp was performed for 90 minutes, followed by euglycemic (100 mg/dL) hyperinsulinemic (100 μU/mL) clamp for 90-120 minutes using AP. AP and CGM values were compared with PG values using Parkes consensus error grid during the study period.

AP values were significantly lower than PG values at 5, 30 minute during hyperglycemic clamp. In comparison, CGM value at 0 minute was significantly higher, and its following values except 45 minutes were significantly lower than PG values. The time delay of AP and CGM values to reach maximum glucose levels were 5.0 ± 22.3 and 28.6 ± 32.5 min, respectively. There were no significant differences between CGM, AP and PG values during euglycemic hyperinsulinemic clamp. The accuracy of CGM was significantly lower during plateau periods compared to glucose decreasing period in the first 60 minutes of euglycemic hyperinsulinemic clamp. Ninety nine percent of CGM and AP values were within the zone A and B in the Parkes consensus error grid. CGM and AP were almost acceptable in the view of clinical usage. Both CGM and AP were unable to follow accurate plasma glucose values during non-physiologically rapid glucose rising, however, indicated acceptably accurate values during physiological glucose change.

Supported By: Nikkiso

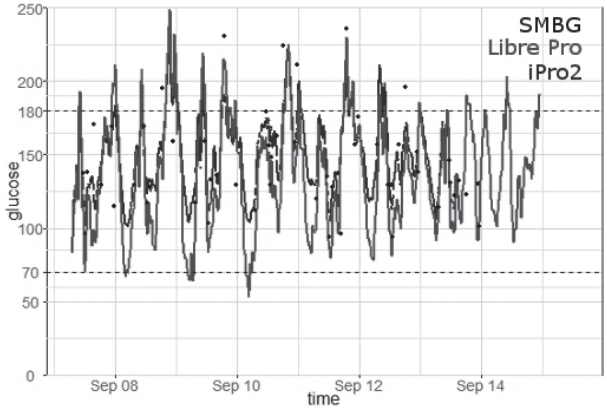
896-P

Comparison of the New Factory Calibrated Sensor with Existing CGM Sensor

JOTHYDEV KESAVADEV, PRADEEP BABU SADASIVAN PILLAI, ARUN SHANKAR, ASHWIN DAVID ASHOK, GEETHU SANAL, REMYA IYER, GOPIKA KRISHNAN, SUNITHA JOTHYDEV, *Trivandrum, India*

Clinicians use CGM to examine trends of glucose levels to beyond those possible by SMBG, to make informed decisions about treatment regimens. Therefore, the reliability of CGM devices available in the market is of utmost importance. In the first study of its kind, we compared simultaneously done CGM readings of 2 available devices, iPro2 and LibrePro (approved in India in March 2015), as a pilot study in two each of type 2 diabetes, type 1 diabetes, gestational diabetes, prediabetes and normal subjects after informed consent and EC approval. iPro2 uses SMBG to calibrate the readings and can be used for up to 7 days, whereas LibrePro is a factory-calibrated device with longer (14 days) analysis possible. We discarded the first 24 hr readings and compared overlapping time zones of the two devices with graphical and statistical analysis. Both provided similar trends. Substantial variability in readings was noted in 6 out of 10 subjects with either variations near maximum and minimum glucose values (Figure 1) or in baseline levels altogether. The difference in readings are substantial enough to alter clinical management. This study demonstrated that the monitoring ability of LibrePro and iPro2 does not appear comparable and larger studies are needed to prove its accuracy in different types and stages of diabetes or prediabetes so as to obtain glucose values comparable to that of glucose meters for error free clinical decision making.

Figure 1.



897-P

Accuracy of a Fourth-Generation Glucose Sensor Throughout Its Functional Life

RON BRAZG, MARK CHRISTIANSEN, BRUCE W. BODE, TIMOTHY S. BAILEY, SATISH GARG, ROBERT SLOVER, SUIYING HUANG, JOHN SHIN, SCOTT W. LEE, *Renton, WA, Walnut Creek, CA, Atlanta, GA, Escondido, CA, Denver, CO, Aurora, CO, Northridge, CA*

A fourth-generation subcutaneous glucose sensor was evaluated in subjects aged 15-75 years for 7 days of continuous wear. Its accuracy was determined throughout its functional life by comparing sensor glucose (SG) values with reference plasma glucose values (YSI) during frequent sample testing (FST) on days 1, 3, and 7. Data were transmitted from the sensors to

For author disclosure information, see page A696.

either a MiniMed 640G pump or to a smartphone app. Eighty-nine subjects were enrolled and 82 completed the study. All sensors were worn on the abdomen. A total of 12,090 paired SG-YSI values were available from the pump and 11,619 from the app. The overall mean absolute relative difference (MARD) was 10.6±9.62% for the 640G pump and 10.4±10.39% for the app; overall precision (640G vs. app) was 8.4±9.93%. Mean and median MARD values for each FST and each device are shown in the Table. The overall within-20% agreement rate between YSI and SG values (or within 20 mg/dL for YSI values ≤80 mg/dL) was 88.2% for the pump and 89.5% for the app. The fourth-generation glucose sensor showed excellent accuracy and precision throughout its functional life with either the 640G pump or smartphone app. These results support use of this sensor in standalone, open-loop, and closed-loop systems over the course of 7 days.

Table. Fourth-Generation Glucose Sensor Accuracy by Day.

FST Day	Device	N	MARD, % Mean ± SD	MARD, % Median
Day 1	Pump	4294	13.0 ± 11.07	10.2
	App	4013	12.4 ± 11.13	9.3
Day 3	Pump	4533	8.9 ± 7.97	6.9
	App	4294	8.7 ± 8.13	6.5
Day 7	Pump	3263	9.5 ± 8.97	6.8
	App	3312	10.1 ± 11.60	7.4

Supported By: Medtronic

898-P

Accuracy Evaluation of Six Blood Glucose Monitoring Systems often Used with Insulin Pumps following ISO 15197, Section 6.3

GUIDO FRECKMANN, NINA JENDRIKE, ANNETTE BAUMSTARK, STEFAN PLEUS, CORNELIA HAUG, *Ulm, Germany*

Analytical accuracy of 6 BGMS often used with insulin pumps was evaluated in this study. For such BGMS, accuracy is especially important, as it may directly influence therapeutic decisions.

Capillary blood samples from 100 different subjects were measured with 3 reagent system lots of each of the BGMS (Accu-Chek Aviva Nano [A], Accu-Chek Mobile [B], Accu-Chek Performa Nano [C], Contour Next Link 2.4 [D], FreeStyle Lite [E] and OneTouch Verio IQ [F]) and 2 different comparison methods (glucose oxidase [GOD] and hexokinase [HK], both traceable according to ISO 17511) following procedures described in ISO 15197:2013 section 6.3. Deviations between BGMS and comparison measurement results were then calculated. According to ISO 15197:2013, accuracy of a BGMS is regarded acceptable if for each of the 3 lots at least 95% of the values measured with the BGMS are within ±15 mg/dl of the comparison measurements at glucose concentrations <100 mg/dl and within ±15% at glucose concentrations ≥100 mg/dl and if at least 99% of all results fall within zones A and B of the Consensus Error Grid.

Evaluated against the two comparison method, 5 of 6 systems each met the criteria mentioned above. For GOD method these were systems A, B, C, D, E, and for HK method these were systems A, B, C, D and F. More stringent limits (±10 mg/dl, respectively ±10%) were met by system D regardless of the comparison method.

Not all of the BGMS often used with insulin pumps showed the same level of accuracy in this study. Depending on the comparison method applied, 1 system each could not fulfill accuracy requirements of ISO 15197:2013. Especially when blood glucose values are directly used to calculate the required insulin dose, high accuracy is important to ensure a safe and adequate therapy.

Supported By: Bayer Vital GmbH, Germany

899-P

Clinical Performance of One Touch Verio Blood Glucose Monitoring Systems

STEVEN J. SETFORD, STEPHEN MACKINTOSH, STUART PHILLIPS, HILARY CAMERON, LESLEY MILLER, *Inverness, United Kingdom, Wayne, PA*

The One Touch Verio blood glucose test strip was launched in 2010. The system accuracy of randomly selected manufactured batches has been routinely assessed on diabetes subjects in clinic. Over the period 2010-2015, system accuracy was ≥97.35% of all strips tested by year, meeting the ISO 15197:2013 accuracy requirement (≥95% of values to be within 15mg/dL or 15% of reference, at <100 mg/dL or ≥100mg/dL glucose respectively; see Table). 99.99% of points were within zones A and B of the consensus error grid for type 1 diabetes. Clinic data comprises 63,023 data points providing an unparalleled assessment of the performance of a commercially available blood glucose test strip and associated meters.

Verio strip accuracy is a function of strip design, in which thin film palladium and gold electrodes are arranged in a co-facial manner, defining the lower and upper walls of the sample chamber. Reagents, deposited on the lower electrode, rapidly dissolve in contact with applied sample, the enzyme reaction providing glucose specificity, with diffusion of a redox species between the electrodes, coupled to a complex waveform and algorithm acting to minimize interferences in the blood, notably hematocrit.

Table.

Year	In spec 12/15	In spec 15/15	N	Percent in spec 12 mg/15%	Percent in spec 15mg/15%
2010	7994	8029	8179	97.74	98.17
2011	15915	15996	16432	96.85	97.35
2012	12209	12225	12469	97.91	98.04
2013	13733	13766	14053	97.72	97.96
2014	9737	9744	9880	98.55	98.62
2015	1977	1982	2010	98.36	98.61
2010-2015	61565	61742	63023	97.69	97.97

900-P

Patient Empowerment Using the MyStar Extra Device at Office-based Physicians: Results of the MyStarT Study

BERNHARD KULZER, HELMUT ANDERTEN, ANJA BORCK, GUIDO FRECKMANN, *Bad Mergentheim, Germany, Hildesheim, Germany, Berlin, Germany, Ulm, Germany*

Background: Blood glucose (BG) self-monitoring provides important information to patients with diabetes. MyStar Extra (Sanofi) is a recently introduced device that, in addition to BG determinations, estimates HbA1c values. The goal of this study was to measure if the use of this device results in improved patient empowerment.

Methods: MyStarT is a non-interventional study conducted at office based physicians across Germany. Adult patients were included, given that they had newly received the MyStar Extra device. Patients completed the "Diabetes Empowerment Scale" (DES; Anderson et al. 2000) at baseline and the 24-week follow-up. This questionnaire is intended to measure the psychosocial self-efficacy of people with diabetes asking questions for different items (e.g., need for change, developing a plan, overcoming barriers, asking for support, motivating oneself and others).

Results: A total of 1,797 patients were included of which 1,521 patients had a complete follow-up (85%). Patients had a mean age of 60.3±14.0 years, 56.1% were male, the mean body weight was 90.8±20.2 kg, and 13.8% has type 1 and 86.0% type 2 diabetes. At the 24-week follow-up, the HbA1c was reduced by a mean of 0.34±3.28% from 7.7±1.9% at baseline. The DES score (n=1,353) increased from a baseline value of 29.9±6.4 to a 24-week value of 31.9±5.9, reflecting an increase of 2.05 points (95% CI 1.73 to 2.37; p<0.0001). In a multivariable regression analysis, the improved HbA1c was associated with improved patients empowerment (p<0.0001).

Conclusions: This study using a BG meter that provides estimated HbA1c values in addition to blood glucose measurements found improved HbA1c control and improved patient empowerment. Both variables were shown to be associated in a stepwise multivariable regression analysis.

Supported By: Sanofi-Aventis Deutschland GmbH

901-P

Accuracy of a Fourth-Generation Glucose Sensor Paired with Different Real-Time Display Devices

MARK CHRISTIANSEN, RON BRAZG, TIMOTHY S. BAILEY, BRUCE BODE, ROBERT H. SLOVER, SATISH GARG, SCOTT W. LEE, JOHN SHIN, FRANCINE R. KAUFMAN, *Walnut Creek, CA, Renton, WA, Escondido, CA, Atlanta, GA, Aurora, CO, Denver, CO, Northridge, CA*

A fourth-generation glucose sensor was paired with two different devices to determine its accuracy and suitability for use. After a 7-day run-in phase, subjects wore sensors attached to transmitters specific for either the MiniMed 640G insulin pump or a smartphone app. Subjects underwent 12-hour in-clinic visits on study days 1, 3, and 7 for frequent sampling of plasma glucose using YSI as the reference. Sensor glucose (SG) and YSI values were compared for accuracy analyses. Eighty-nine subjects were enrolled and 82 completed the study. A total of 12,090 paired YSI-SG points were available from the 640G pumps and 11,619 from the smartphone app. Clarke Error Grid analysis showed 99.1% of the paired points in the A+B zones for each dataset. Mean within-30% and within-20% agreement rates are provided in the Table for YSI values in various ranges. For reference values ≤75 mg/dL, the 30% agreement rate is within 22.5 mg/dL and the 20% agreement rate

is within 15 mg/dL. The overall within-20% agreement rate between YSI and SG values (or within 20 mg/dL for YSI values ≤80 mg/dL) was 88.2% for the pump and 89.5% for the app. Agreement rates were higher with the smartphone app and tended to improve with increasing glucose levels. Results support use of this sensor for standalone, open-loop, and closed-loop systems.

Table. Fourth-Generation Glucose Sensor Accuracy by Glucose Concentration Range.

	640G Pump		Smartphone App	
YSI Reference Range	Within-30% Agreement Rate	Within-20% Agreement Rate	Within-30% Agreement Rate	Within-20% Agreement Rate
≤75 mg/dL	90.5%	72.7%	93.0%	76.3%
>75 to 180 mg/dL	93.4%	84.3%	94.7%	86.6%
>180 mg/dL	95.6%	89.1%	97.0%	90.8%

902-P

The Effect of Real-Time Continuous Glucose Monitoring (RT-CGM) in Prediabetes

ALICIA WARNOCK, SARA SALKIND, SHERI SENICKI, STEPHANIE FONDA, SUSAN WALKER, WILLIAM POLONSKY, DAVID RODBARD, ROBERT VIGERSKY, *Bethesda, MD, San Diego, CA, Potomac, MD*

We performed a prospective, two-arm, parallel group study in 70 subjects with advanced prediabetes (FPG 110-124 mg/dL and/or A1c 6.0-6.4%) to compare glycemic control after 3-months of RT-CGM (2 wks "on"/1 wk "off" in 4 cycles) to "usual care" following a 3-month "wash-in" period in which diabetes education was provided at baseline (1 hr with R.D. and 2 hrs of classroom). Thirty-one subjects (15 "usual care"/16 RT-CGM) were followed clinically for an additional 12 months. Clinical and laboratory data were obtained at baseline, 6 months and 18 months. Metrics of glycemic variability (GV) were obtained using DexComG4 Pro ("masked") at baseline and 6 months (Table 1).

Conclusion: There were no significant differences in clinical, laboratory or GV metrics between baseline and 6 months within or between groups. In addition, there were no differences in clinical parameters at 18 months. Focus groups of participants using RT-CGM uncovered a wide heterogeneity of device engagement, understanding, and general knowledge about prediabetes. Given these observations and the fact that our study design did not specifically educate subjects about CGM patterns, we recommend future CGM studies in prediabetes include education on interpreting CGM data and on mitigating GV with appropriate lifestyle modifications in conjunction with a structured behavioral framework and personalized support.

Table 1.

		N	Baseline Mean (SD)	N	6 months Mean (SD)	Average Difference Baseline – 6 months (SD)
Standard of Care	BMI (kg/m^2)	36	31.37 (5.19)	27	31.27 (6.04)	-0.23 (0.95)
	A1C (%)		6.08 (0.27)		5.93 (0.35)	-0.39 (1.18)
	FPG (mg/dL)		108.97 (14.70)		101.63 (8.63)	-5.89 (11.13)
	2^h OGTT* (mg/dL)		120.78 (43.51)			
	Mean (mg/dL)	34	115.05 (12.55)	11	116.31 (9.77)	-3.05 (5.64)
	SD (mg/dL)		22.48 (7.37)		22.13 (4.94)	0.81 (17.70)
	CV (%)		22.94 (10.99)		24.08 (10.12)	1.14 (15.21)
Standard of Care + RT-CGM	BMI (kg/m^2)	34	29.08 (4.61)	32	28.52 (4.47)	-0.52 (1.28)
	A1C (%)		5.99 (0.23)		5.97 (0.27)	-0.03 (0.31)
	FPG (mg/dL)		108.65 (12.34)		102.06 (12.45)	-6.84 (14.25)
	2^h OGTT* (mg/dL)		131.21 (35.49)			
	Mean (mg/dL)	28	117.30 (11.85)	7	107.22 (7.82)	1.46 (9.51)
	SD (mg/dL)		25.76 (9.84)		16.41 (13.65)	0.79 (4.57)
	CV (%)		18.48 (4.94)		18.26 (3.00)	0.36 (3.84)

903-P

Clinical Significance of Glycated Albumin (GA) in Diabetic Patients with Liver Cirrhosis

SOO MIN HONG, SUNG-WOON KIM, JEONG-TAEK WOO, SUK CHON, SANG YOUL RHEE, SEUNGJOON OH, *Seoul, Republic of Korea*

HbA1c may not reflect correct glycemic state in diabetic patients with liver cirrhosis. The aim of this study is to evaluate the disparity between HbA1c and GA. Total 95 diabetic patients with liver cirrhosis were reviewed by records who visited the departments of endocrinology and gastroenterology in Kyung Hee University Hospital. We assessed random glucose level, HbA1c, GA and other baseline characteristic parameters. The mean GA level was 25.42±9.23% in 95 diabetic patients with liver cirrhosis. By conversion equation, (CH Jung et al. Plos one 2014; 9 (4): e95729) the corresponding HbA1c level must be 9.42±2.48%. However, it was underestimated as 7.46±1.72% in this population ($p < 0.0001$). In regard to anemia, the mean GA level in Hb < 10mg/dL group and Hb ≥ 10mg/dL group was similar (26.23±6.88% vs. 25.32±9.49%, $p = 0.44$). However, the mean HbA1c level was significantly lower in Hb < 10mg/dL group than in Hb ≥ 10mg/dL group (6.34±1.47% vs. 7.59±1.7%, $p = 0.04$). In regard to hypoalbuminemia, the mean HbA1c level in albumin < 3.5 mg/dL group and albumin ≥ 3.5 mg/dL group was similar (7.11±1.8% vs. 7.55±1.7%, $p = 0.21$). The mean GA level was also similar in albumin < 3.5 mg/dL group and albumin ≥ 3.5 mg/dL group (29.26±10.76% vs. 24.46±8.62%, $p = 0.07$). HbA1c alone was not enough an indicator to evaluate glycemic state in diabetic patients with liver cirrhosis. GA showed no significant difference both in anemia group and in hypoalbuminemia group. Thus, we found GA to be a useful glycemic index in diabetic patients with liver cirrhosis, especially in those accompanied with anemia.

904-P

Current Situation of Self-Monitoring of Blood Glucose in Insulin-Naïve Patients with Type 2 Diabetes in China

YINGYING LUO, BAO YUQIAN, PUHONG ZHANG, WEIPING JIA, LINONG JI, *Beijing, China, Shanghai, China*

Objective: To investigate the current situation of SMBG (self-monitoring of blood glucose) in insulin naive patients with type 2 diabetes in China.

Methods: The data we analyzed is from ORBIT study. The ORBIT study was an 6-month observational study which was designed to evaluate the effect of initiation of basal insulin in real world setting in China. Type 2 diabetic patients who had a HbA1c>7% on oral agents and had been put on basal insulin were recruited. There were three visits at a 3-month interval. SMBG frequency, glucose level, hypoglycemia were recorded at each visit. We firstly describe the frequency of SMBG at each visit. Then we divided all the participants into three groups (low, middle, high SMBG frequency group) according to their SMBG frequency (0, 1-5, ≥6 times per month) and compared the difference of clinical outcome among groups.

Results: 18995 patients were enrolled into the study. The mean self-reported frequency of SMBG at each visit is only 5±10, 7±10 and 6±8 times per month. At visit 3, patients in high SMBG frequency group have the highest HbA1c control (HbA1c≤7%) rate at 44.9%, while the HbA1c control rate among patients in middle and low SMBG frequency group are 39.0% and 36.1%. Similarly, the HbA1c level of patients in high SMBG frequency group at visit 3 is 7.3%, which is the lowest one among three groups. However, a positive relationship is seen between SMBG frequency and hypoglycemia rate. The self-reported hypoglycemia rate at visit 3 in high SMBG frequency group is 11.1%, which is higher than that in middle and low SMBG frequency group (9.4% and 4.1%, respectively).

Conclusion: In real world practice, the frequency of SMBG in insulin naive type 2 diabetic patients in China is very low and is much lower than it is recommended in Chinese guideline. Nevertheless, in our study, we still see that more frequent monitoring of blood glucose may lead to a better glucose control. Those who have a higher SMBG frequency seems to be the patients who are more likely to develop hypoglycemia.

905-P

Fifth-Generation Glucose Sensor System with Extended Wear and Fewer Calibrations

JOHANNA ULLOA, ANDREA VARSAVSKY, RAGHAVENDHAR GAUTHAM, INDU PREMAKUMAR, *Northridge, CA*

The fifth generation sensor is a novel, 10 day wear, subcutaneous glucose oxidase-based sensor. This sensor incorporates redundant electrochemical sensing elements with diagnostics, fault detection and a custom algorithm to allow for improvements in accuracy, reliability and sensor longevity with 1 calibration per day. Data from an ongoing human feasibility clinical trial were analyzed to demonstrate these advances.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

The feasibility clinical trial was designed such that subjects with type 1 and type 2 diabetes wear up to 4 sensors in the arm and abdomen for a period of 10 days. Participants take daily reference blood glucose values using the Bayer® CONTOUR® NEXT LINK RF Blood Glucose Meter and participate in 3 in-clinic sessions where meal challenges are administered and blood glucose values are recorded every 15 minutes for 3-4 hours. Data collected thus far were retrospectively processed relative to reference SMBG's with 1 calibration per day and sensors with gross mechanical failures were excluded from the analysis.

Sensor design, diagnostics and algorithm improvements show strong performance into day 10 with 1 calibration per day. Thus far, results for sensors worn in the arm and abdomen have yielded overall MARD of 10.8% vs. SMBG and a 40/40 agreement rate of 98.4% (55 sensors and 5710 evaluation points); sensors worn in the arm have yielded overall MARD of 9.8% vs. SMBG and 40/40 agreement rate of 99.1% (26 sensors and 2662 evaluation points).

Preliminary clinical data for the fifth generation glucose sensor suggest strong performance with minimal calibrations and for a wear duration period of 10 days. Evaluation is ongoing.

906-P

Strengths and Limitations of New Approaches for Graphical Presentation of Blood Glucose Monitoring System Accuracy Data

STEFAN PLEUS, FRANK FLACKE, JOCHEN SIEBER, CORNELIA HAUG, GUIDO FRECKMANN, *Ulm, Germany, Frankfurt, Germany*

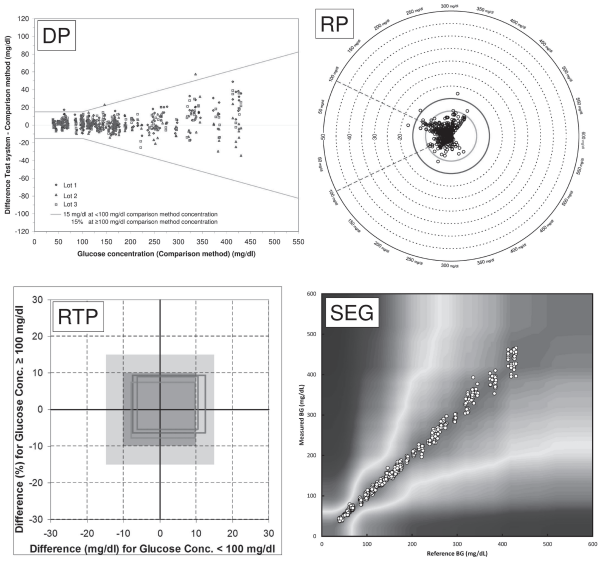
System accuracy evaluations of blood glucose monitoring systems (BGMS) typically include graphical presentations such as traditional difference plots (DPs). 3 new approaches were recently presented: radar plots (RPs), rectangle target plots (RTPs), and surveillance error grids (SEGs).

Data from 3 system accuracy evaluations (2× BGStar, 1× MyStar Extra; Agamatrix Inc., Salem, NH) were analyzed in RPs, RTPs, and SEGs (example in Figure). These new plots were compared with traditional DPs to establish their respective strengths and limitations.

Plots with individual data points (DPs, RPs, SEGs) allow for more detailed assessment of data than RTPs, in which data are sorted into 1 of 2 categories (< 100 mg/dL or ≥ 100 mg/dL) and then averaged. DPs and RPs become harder to read with increasing numbers of data points, whereas RTPs are not affected, so showing and comparing data from different BGMS is easier. RTPs also provide more easily accessible information about trueness and precision (location and size of the rectangle). SEGs have the advantage of having many data points and also provide risk estimation. Overall assessment of accuracy may be easier in RPs or RTPs, because a small size of the data point cluster or rectangle indicates high accuracy.

The types of plots have different strengths and limitations, and the selection of a specific type depends mostly on the kind of information sought.

Figure.



Supported By: Sanofi-Aventis France

907-P

Medication Interference with Continuous Glucose Monitoring Devices: Implications for the Artificial Endocrine Pancreas

MICHAEL SLAMA, SONA VEETTIL, BARBARA NORBY, CHERYL SHONKWILER, ANANDA BASU, RITA BASU, *Rochester, MN*

There is limited data regarding interference of CGM with prescribed medications in type 1 diabetes (T1D). Accuracy and reliability of glucose sensing by the CGM is vital and a necessary prerequisite of an effective artificial endocrine pancreas (AEP) system; hence better understanding of whether drugs interfere with glucose sensors is critical for safe translation of the AEP efforts into clinical practice. We have previously published that acetaminophen interferes with some CGM devices. The current study was designed to systematically investigate the responses of several commercially available CGM systems (Dexcom SevenPlus™, Medtronic Guardian, Dexcom G4 Platinum, Abbott Libre) to single administration of drug in 10 nondiabetic healthy drug naïve volunteers. The study was set up as a Simon 2 step design. If minimal/no interference observed in 4 subjects that drug was eliminated from further testing. Preliminary data is presented in the Table below and suggests certain drugs interfere with CGM's on account of their volume of distribution/shifting working potential of the CGM. Interstitial fluid samples are being analyzed for concentration of drug to directly correlate with interference patterns observed when compared to plasma glucose. Future studies are required to test interference of multiple doses of drugs and newer CGM's that are made available for testing.

Table.

Name of the Drug	Dose	Number of subjects studied (N)	CGM interference pattern
Albuterol	4 mg	N=4	↔ ↑
Ascorbic acid	1000 mg	N=3	↔
Atenolol	100mg	N=4	↔
5-amino salicylic acid	1000 mg	N=4	↔ ↑
Acetyl cysteine	1200mg	N=4	↔
Acetaminophen	1000 mg	N=9	↑
Gemfibrozil	600 mg	N=4	↔
Hydrochlorothiazide	50 mg	N=4	↔
Lipitor	40 mg	N=4	↔
Lisinopril	20 mg	N=8	↑
Losartan	50mg	N=4	↔
Wine	374 ml	N=9	↑

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908-P

Glycemic Benefits of a Long-Term Implantable Glucose Sensor in the PRECISE Study

PRATIK CHOUDHARY, J. HANS DEVRIES, JORT KROPFF, SANKALPA NEUPANE, STEVE C. BAIN, CHRISTOPH KAPITZA, THOMAS A. FORST, MANUELA LINK, RAVI RASTOGI, XIAOXIAO CHEN, *London, United Kingdom, Amsterdam, Netherlands, Cambridge, United Kingdom, Swansea, United Kingdom, Neuss, Germany, Mainz, Germany, Ulm, Germany, Germantown, MD*

This abstract presents the changes in HbA1c and time in hypoglycemia in the PRECISE study, which studied a new long-term implantable continuous glucose monitoring (CGM) system through a 180-day accuracy trial.

The Eversense® System (Senseonics Inc., U.S.) is composed of an implantable, fluorescence-based glucose sensor and a wearable transmitter that wirelessly communicates with a mobile app to display glucose values, trends, and alarms. In this prospective, single-arm investigation, 71 adult subjects with T1DM and T2DM were enrolled at 7 clinical sites. Subjects used the CGM system at home and in-clinic. During the study, HbA1c was measured at the screening visit, day 90 visit, and day 180 visit. Hypoglycemia episodes were quantified by the percent time when the CGM glucose was less than 70 mg/dL. For the full 180-day enrollment, the median CGM wear duration was found to be 23.5 hours/day with 25th percentile 23.0 hours/day.

The clinical outcomes of the CGM system were evaluated by changes in HbA1c on day 90 and day 180 visits compared to the screening visit and by percentage time in hypoglycemia during the 1st, 3rd, and 6th month at-home use. In a completers' analysis, 27 subjects that entered month 6 of CGM wear and had all three HbA1c measurements were included. The average HbA1c decreased from 7.5% (SD=1.3%) to 7.1% (SD=1.0%) on day 90, which was maintained till the end of the 180-day study at 7.2% (SD=1.0%)

[repeated measures ANOVA, p=0.0003]. The average percent time in hypoglycemia numerically decreased from 5.2% (SD=3.3%) in month 1 to 4.8% (SD=3.4%) in month 3 and further to 4.2% (SD=3.8%) in month 6 (repeated measures ANOVA, p=0.1265).

Overall, the use of a new implantable glucose sensor was found to be associated with decreased HbA1c together with numerical reduction in time in hypoglycemia in a 180 day study.

909-P

In Vitro Proof of Principle Experiment with the Osmotic Pressure-based Sencell Implantable Glucose Sensor Technology

SANJA RAMLJAK, BERND LECHER, ANJA MEIER, EUGENE VAN WYK, SHOAN WATSON, RUNE FRISVOLD, ANDREAS PFÜTZNER, *Mainz, Germany, Wendelsheim, Germany, Cambridge, United Kingdom, Bergen, Norway*

Minimally invasive or implantable continuous glucose monitoring systems have become available and are increasingly adopted. A novel implantable glucose affinity biosensor (Sencell, LifeCare, Norway) is based on competitive and reversible binding of glucose and polysaccharide dextrane to the glucose specific lectin concavalin A (ConA). The Sencell technology uses osmotic pressure difference arising between a reagent chamber (containing active fluid with ConA and dextrane) and a diffusion chamber (in direct contact with interstitial fluid) to determine interstitial glucose concentrations. Both chambers are separated by a nanoporous membrane permeable to glucose and water, but not to ConA or dextrane. Because the skin anatomy of pigs markedly resemble the human situation, we performed a first proof-of-principle experiment in this animal model using a wired device prototype. Implantation of four Sencell sensors and one Dexcom® G4 control sensor was performed in the back and the neck area of three pigs (one female, two male), respectively. Subsequently, they received an oral glucose load of 75 to 150 g of dextrose. Reference measurements from capillary blood samples were performed using the YSI 2300 STAT Plus glucose analyser every 15 min for 5 h. Several Sencell prototype devices were able to track glucose changes, especially when blood glucose levels exceeded 200 mg/dL. The magnitude of the signals was in a predicted range and working sensors were matching G4 results and displayed a lag phase of 20 minutes vs. plasma reference glucose. Although the body temperatures in the animals within three experimental days partially exceeded 39°C, the activity of ConA was preserved. No external signs of inflammation were observed in the histology examinations. In conclusion, Sencell proof-of-principle has been demonstrated in vivo.

Supported By: Lifecare A/S

910-P

Xylose Substantially Interferes with Some Glucose-dehydrogenase-based Blood Glucose Meters for Patient Self-Testing

ANDREAS PFÜTZNER, FILIZ DEMIRCIK, DANIELA SACHSENHEIMER, JAN SPATZ, SANJA RAMLJAK, ANKE H. PFÜTZNER, *Mainz, Germany*

Some blood glucose strips based on glucose-dehydrogenase (GDH) are subject to interference of xylose. This issue is not considered to have major importance in daily life, because an uptake of up to 25g of xylose only occurrs during a gastrointestinal malabsorption test, and only a fraction of xylose levels are wrongly displayed as a glucose signal. However, recent developments in the food insdustry include an increased use of xylose, e.g., from edible algae, in so-called "functional food." Our goal was to explore the extent of xylose-interference on commercially available blood glucose meters (BGM). Fresh whole blood was drawn from a healthy donor and manipulated to contain 3 different glucose concentrations (50-80 mg/dL, 130-160 mg/dL, and 250-300 mg/dL). The samples were spiked to contain 0, 25, 50, and 100 mg/dL of xylose. Each sample was measured 3 times with 2 different strip lots using the following devices in parallel: AccuChek Aviva, AccuChek Connect, Contour Next, FreeStyle Freedom Lite, FreeStyle Insulinx, MyStar Extra, OneTouch Verio IQ, and Wellion Calla, with YSI as the reference method taken before and after the tests. Four of the devices showed no interference with xylose. The mean absolute deviation was e.g., with 50 mg/dL xylose at low/mid (high glucose levels was 2/-1/-1 mg/dL with AccuChek Aviva, 1/-4/9 mg/dL with AccuChek Connect, 52/41/58 mg/dL with Contour Next, 57/47/51 mg/dL with FreeStyle Freedom Lite, 58/66/55 mg/dL with FreeStyle Insulinx, 10/12/11 mg/dL with MyStar Extra, 75/76/92 mg/dL with OneTouch Verio IQ, and 7/9/8 mg/dL with Wellion Calla. The xylose interference in BGM based on common GDH technologies was 100% aditive to the glucose reading, and thus much more pronounced than described in the literature, while systems using other technologies were not subject to this influence. With current changes in food processing introducing more xylose into food products, these findings may become relevant for diabetes patients in real life.

Supported By: Sanofi Diabetes

911-P

Advantages of Glucose Monitoring with Implantable Telemetry in Freely Moving Conscious Nonhuman Primates

BINGDI WANG, WEI QIAO, GUOFENG SUN, YONGQIANG LIU, JIQIU QIAO, WEI-WEI YI, HUI WANG, XIAOLI WANG, RYAN LINDQUIST, YIXIN (JIM) WANG, YONG-FU XIAO, *Taicang, China, Saint Paul, MN*

Long-term glucose monitor is challenging. This study was to investigate telemetry monitor of blood glucose in normoglycemia and diabetes cynomolgus monkeys (n=5). Each monkey was subcutenusly implanted with a HD-XG transmitter (DSI, USA) with its glucose sensor being placed in a femoral artery. Blood glucose, body temperature and physical activity were remotely monitored for ≥8 weeks. Diabetes assays, ivGTT, oGTT, ITT, GGI and clamp, were tested. The telemetry glucose results correlated well with the glucometer readings (Figure 1A). The ivGTT data showed that the glucometer and telemetry readings were very similar in both normol and diabetic monkeys, even with dual ivGTTs consecutively (Figure 1B). Glucose clamp results also showed high matches between the 2 methods (Figure 1C). However, the advantages of monitoring blood glucose by the telemetry method are: 1.) consecutive data collection (day and night); 2.) no bleeding requirement; 3.) no restriction (moving freely); 4.) no anesthesia needed; 5.) no stress and disturbance; 6.) less labor intensity during ivGTT and clamp; 7.) recording natural response, such as circadian and postprandial effects; 8.) instant outcomes without lab test. Our data demonstrate that the telemetry method can monitor blood glucose remotely and continuously in conscious, stress-free, freely moving monkeys, which may bring advantages in diabetes research and drug discovery.

Figure 1.

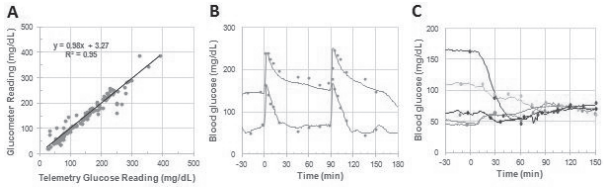


Figure 1. Comparison of the outcomes measured by glucometer and telemetry. *A*, The correlation of the blood glucose levels measured by the glucometer and telemetry. *B*, Blood glucose levels responded to dual ivGTTs in one normoglycemia (Blue) and one diabetes (Green) monkeys measured with both telemetry (solid line) or glucometer (solid dotted circles). *C*, Hyperinsulinic-euroglycemic clamps in normoglycemia (n=3) and diabetes (n=2) monkeys with similar glucose levels measured by telemetry (solid line) and glucometer (solid dotted circles) in each monkey (per color/per monkey, n=5).

912-P

Innovative Use of Point-of-Care Capillary Glucose Monitoring to Reduce Inpatient Hypoglycaemia

GERRY RAYMAN, CHRIS KERRY, ANNE SCOTT, RAJESH RAJENDRAN, *Ipswich, United Kingdom*

Approximately 10% of diabetes inpatients have a severe hypoglycaemic episode and ~2% need rescuing with IV glucose (UK National Diabetes Inpatient Audit 2013). Inpatient hypoglycaemia is associated with an increased length of stay and a 2-3 fold increase in mortality. Remote monitoring of Abbott Precision Xceed Pro™ Web Point Of Care (POC) meters (Abbott Diabetes Care Inc., Alameda, CA, U.S.) was developed to facilitate central laboratories to quality control ward based meters and individual users. We considered that with modification an "alert" system could be developed to enable diabetes teams to quickly identify patients experiencing hypoglycaemia, particularly first events to prevent recurrence. With IT support from Abbott Diabetes Care UK we were able to link Capillary Blood Glucose (CBG) data with patients' unique identifiers, ward location, date and time. We assessed the impact of this innovation by comparing first and subsequent CBG ≤3 and <2.2mmol/l, before (2012) and after (2013-14) introduction. Admissions numbers were unchanged but there was a decline in first hypoglycaemic events ≤3mmol/l; (676, 612 and 575 for 2012, 2013, 2014 respectively, 14.9% reduction 2012 vs. 2014). The reduction was even greater for more severe events ≤2.2mmol/l; 210, 139 and 132 for 2012, 2013, 2014 respectively, 37.1% reduction 2012 vs. 2014. Recurrent hypoglycaemia (results ≤3) fell dramatically (p<0.001) from 228 to 97/yr (2012 vs. 2013; 57.5% reduction) and 42/yr (2012 vs. 2014; 81.5% reduction) as did more severe (<2.2) recurrent events from 77 to 27/yr (2012 vs. 2013; 64.9% reduction) and 16/yr (2012 vs. 2014; 79.2% reduction). As expected there was a small increase in mean CBG (8.7 to 8.9mmol/l) however this was not at the expense of significant hyperglycaemia as there was actually a 24.9% fall in CBG≥20.0mmol/l. This study demonstrates that adapting remote monitoring of POC CBG systems for clinical use can be highly effective in preventing first and recurrent hypoglycaemia in inpatients with diabetes.

For author disclosure information, see page A696.

913-P

Improved Glycemic Control in a Patient Group Performing 7-Point Profile Self-Monitoring of Blood Glucose and Intensive Data Documentation

JOCHEN SIEBER, FRANK FLACKE, MANUELA LINK, CORNELIA HAUG, GUIDO FRECKMANN, *Frankfurt, Germany, Ulm, Germany*

Regular self-monitoring of blood glucose (SMBG) is recommended for all diabetes patients treated with insulin as an integral part of their therapy. Current ADA guidelines recommend 4 measurements per day for patients with intensive insulin therapy. In the study presented here, effects of 7-point profile SMBG with a diabetes management system (DMA) were investigated. In an open-label, uncontrolled, multicenter study with a 12-week observational period, 50 patients (25 type 1 [T1D] and 25 type 2 diabetes [T2D] patients) were instructed to measure their blood glucose at least 7 times a day using DMA combined with the iBGStar SMBG system. Patients documented all SMBG results and therapy parameters with the DMA. HbA1c was measured at regular visits at the study sites. Patients reviewed and managed their data as well as their treatment on their own and there were no further assistance or treatment recommendations. After 12 weeks, subjects' mean HbA1c had decreased significantly by 0.46 ± 0.57% ($P < 0.0001$) from 7.51% to 7.05% compared to baseline. There was a difference in HbA1c reduction between T1D (0.27 ± 0.45%) and T2D (0.65 ± 0.62%) patients. HbA1c decrease was higher in patients using basal insulin only (n = 13) (mean decrease 0.80 ± 0.78%; $P = 0.0029$) compared to patients using basal and prandial insulin (n = 36) (0.35 ± 0.44%; $P < 0.0001$). Reduction in HbA1c was not correlated with an increased number of hypoglycemic events (< 55 mg/dL). This observational study showed that glycemic control can be improved by performing 7-point profile SMBG and electronic therapy documentation without any further assistance. We hypothesize that this may be due to increased attention of the patients to their therapy. This was even more pronounced in patients with T2D, and the highest decrease in HbA1c was seen in patients using basal insulin only. These results must be confirmed in a larger and controlled trial but they already strengthen the importance of SMBG in diabetes therapy.

Supported By: Sanofi

914-P

Barriers to Device Uptake in Adults with Type 1 Diabetes (T1D)

MOLLY L. TANENBAUM, SARAH J. HANES, KELLEE M. MILLER, DIANA NARANJO, KOREY K. HOOD, *Palo Alto, CA, Tampa, FL*

Uptake of diabetes devices (insulin pumps; continuous glucose monitors - CGM) continues to be low despite the potential for positive impact on glycemic control and quality of life in people with T1D. As modifiable barriers may influence low uptake rates, we surveyed adults with T1D to 1.) investigate these barriers; 2.) understand profiles of device users vs. non-users and 3.) understand how to focus interventions to increase uptake.

Survey participants were 1503 T1D Exchange participants (M±SD age 35.3±14.8 yrs; dx duration 20.4±12.5 yrs). Scales completed: Diabetes Distress Scale (DDS-T1), Hypoglycemia Fear Survey-Worry Scale, Technology Use Attitudes (General and Diabetes-Specific scales), and Barriers to Device Use.

Though cost was a main concern (57-61% endorsed items), most common modifiable barriers were not liking devices on body (26-47%), and not trusting the technology (17-20%). Younger age was associated with reporting greater number of barriers to using devices (r=-.13 to -.24), p<.001) - in particular, not trusting devices, not wanting attention from others about devices, and daily burden of devices - and reporting more reasons for discontinuing CGM.

The two youngest age groups (18-25; 26-34) reported significantly more barriers to technology use (M 4.3 barriers) than older age groups (35-50; 51-80; M 3.1-3.7). Young adults (18-25) had lowest CGM uptake (26% vs. 40-48% in older groups), more diabetes distress (M 2.2 vs. 1.8-2.1), and higher A1c compared with 26+ year olds (M 8.3% vs. 7.2-7.4). Only in the youngest age group did CGM users have significantly more hypoglycemia worry than non-users of CGM (M 19.5 vs. 16.7). Finally, young adult non-users of CGM had more negative views of diabetes technology, but not general technology, compared with CGM users.

As young adults with T1D report more barriers to device use and lowest rates of CGM use, they should be the focus of future intervention development to address barriers. Interventions should target daily challenges of wearing devices to increase uptake in this age group.

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

915-P

Correlation between Serum Uric Acid and Glycemic Control in Type 2 Diabetes Mellitus

VENKAT RAMESH, DINESHA M., *Mangalore, India*

The relation between serum uric acid and type 2 diabetes mellitus (T2DM) has been a matter of debate since many years. It is known that serum uric acid levels are elevated in patients with early T2DM, and in patients with metabolic syndrome. However, the relation between uric acid and glycemic control has not been fully elucidated, especially in the Indian setup. Positive, negative, and neutral correlations have been observed in different studies. The aim of the present study was to correlate serum uric acid levels with glycemic control in patients with T2DM. This cross-sectional study was conducted on 162 patients with T2DM (without micro or macrovascular complications) attending out-patient clinics. T2DM was defined as per American Diabetes Association guidelines. Patients with renal failure and on drugs that interfered with serum uric acid levels were excluded. Logistic regression analysis was used to evaluate association of uric acid with glycemic control. Mean HbA1c of our study population was 8.37 and only 37% of diabetic patients in our study achieved target HbA1c. We found that there was a negative correlation between serum uric acid and glycemic control in patients with T2DM (after adjusting for confounding factors), and the correlation was statistically significant (N=162, r= -0.522, p=0.001). There was a statistically highly significant difference ($p < 0.001$) in mean serum uric acid levels in patients with well-controlled diabetes i.e., HbA1c ≤7 (mean serum uric acid level: 5.49, Standard deviation (SD): 1.538) and poorly controlled diabetes i.e., HbA1c > 7 (mean serum uric acid level: 3.87, SD 1.635). Our study was limited by its small sample size. These findings strengthen the oft-expressed hypothesis that, in patients with poorly controlled diabetes, glycosuria inhibits the proximal tubular re-absorption of uric acid, leading to lower uric acid levels. Hence, we suggest that, in poorly controlled diabetics, lower cut-off values for hyperuricemia may be applied.

916-P

Fourth-Generation Glucose Sensor for Use in Stand-Alone CGM and Pump Systems

ASHLEY SULLIVAN, MERCEDES PEREZ, JOSEPH HALL, KEITH NOGUEIRA, TALY ENGEL, SCOTT LEE, *Northridge, CA*

The fourth generation sensor is a novel 7 day subcutaneous glucose oxidase-based glucose sensor. The sensor integrates an optimized substrate platform and electrode array designed to improve stability during insertion and extend sensor lifetime. Modifications to the enzymatic layer and sensor chemistries allow for enhanced sensor signal stability and consistency between sensors. The new sensor algorithm enhances the sensor performance and minimizes variability. Changes include proactive diagnostics, preventing the display of unreliable sensor glucose (SG) values and compensation features optimizing performance during the first day of sensor wear. The hardware platforms used for this continuous glucose management (CGM) system allows for the sensor and algorithm to be used in hybrid closed-loop (HCL) and standalone CGM systems. The algorithm can be utilized with transmitters that communicate to an insulin pump with a closed-loop algorithm via a proprietary radio frequency (RF) protocol or to a mobile device operating a display application via Bluetooth Low Energy (BLE) technology. In situations where the CGM is supporting an HCL system, the algorithm in the transmitter includes additional logic that determines if the sensor values are reliable enough for the system to dose insulin. Clinical feasibility studies have demonstrated that the new sensor and algorithm system is reliable enough for insulin delivery in an HCL system and designed with enough flexibility for a standalone CGM system. The system provides consistent and accurate readings as compared to a reference. Clinical studies were conducted using sensors in real-time systems with an insulin pump, mobile display app, and/or a recorder. Sensor data were evaluated against BG points recorded by the meter (5612 evaluation points over 173 sensors). The mean absolute relative difference (MARD) between sensor and BG reference values was 11.24% (12.67% day 1), averaging 2.3 calibrations per day. 98.0% of points met the 40% agreement rate.

917-P

Effect of Continuous Positive Airway Pressure (CPAP) on Glycemic Control and Variability in Type 2 Diabetes (T2D)

ELENA M. MORARIU, EILEEN CHASENS, PATRICK STROLLO, MARY T. KORYTKOWSKI, *Pittsburgh, PA*

Obstructive sleep apnea (OSA) is a common comorbidity of T2D. CPAP improves blood pressure, but the effect on glycemic control is not clear. To investigate this, we compared changes in glycemic control and variability

(GV) in 19 patients with T2D and untreated OSA (apnea hypopnea index (AHI) ≥ 10) randomized to active (n=12) vs. sham CPAP (n=11) for 30 d.

The following measures were obtained: fructosamine (baseline, 30d); 4 x/day blood glucose monitoring (BGM); continuous glucose monitoring (CGM) (Medtronic) 3 d prior and d 27-30 of assigned treatment. GV was determined as standard deviation (SD) and BG range during CGM. No group differences were observed for age (active vs. sham: 58 ± 12 vs. 53 ± 11 y), gender (% male: 46% vs. 57%); BMI (35.5 ± 6.3 vs. 34.9 ± 4.3 kg/m^2), fructosamine, HbA1c (6.6 ± 0.5 vs. 6.9 ± 1.0% [49 vs. 52 mmol/mol)], HOMA IR (3.8 ± 3 vs. 4.8 ± 4.5), or adherence to assigned therapy (4.1 ± 2.9 vs. 4.5 ± 2.7 h). Baseline AHI was higher in the active CPAP group (46.7 ± 29.4 vs. 25.6 ± 11.0, p = 0.04). A moderate effect size was observed for fructosamine in active (261 vs. 253) but not sham (267 vs. 271 umol/L) (Cohen's d = 0.76). Increases in BGM and CGM BG 6A-6P were observed in sham (129 ± 30 vs. 152 ± 35 mg/dl, p = 0.02; 131 ± 36 vs. 147 ± 31 mg/dl) but not active CPAP (148 ± 30 vs. 146 ± 26 mg/dl; 148 ± 24 vs. 153 ± 36 mg/dl, p = 0.6, respectively). No differences were observed for GV in either group (mean difference SD: -2.9 ± 11.1 vs. -3 ± 7.8 mg/dl; Range: -1 ± 66.3 vs. -13 ± 43 mg/dl). In summary, subtle improvements in glycemic control by fructosamine were observed with active CPAP treatment in T2D. The observed deterioration in BGM and CGM with sham treatment was not observed in the active group. No differences were observed in GV in either group. These results suggest a potential differential effect of active CPAP therapy on glycemic control. These results should be interpreted with caution given the small sample size and baseline AHI differences. A larger randomized controlled trial is currently being conducted.

Supported By: National Heart, Lung, and Blood Institute

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULINS

Moderated Poster Discussion: More Insights on Insulin Structure, Duration, Titration, and Biologic Effects *(Posters: 918-P to 925-P), see page 18.*

918-P

Ultrastructural 3D Visualization of Insulin Degludec Multihexamers upon Subcutaneous Injection in Pig

TORBEN SEESTED, ANTHONY BURGESS, CHARLES PYKE, ERICA NISHIMURA, *Måløv, Denmark, Eindhoven, Netherlands*

The ultra-long action of insulin degludec (IDeg) is attributed to self-assembly of insulin di-hexamers into soluble multi-hexamers. Using immuno-gold electron microscopy (iTEM), we have previously confirmed the formation of IDeg multi-hexamers in 2D in the extracellular matrix (ECM) after subcutaneous injection in pigs. In this study, correlative iTEM and focused ion beam scanning electron microscopy (FIB-SEM) was used to visualize the ultrastructural distribution of IDeg multi-hexamers in 3D. For comparison, the distribution of insulin glargine (IGlar) was also visualized. Tissue biopsies were obtained from the neck of a pig 10 min after subcutaneous injection with 20 IU of IDeg U100 (Tresiba) or the U300 formulation of IGlar (Toujeo). The tissue was then embedded into epoxy resin and anti-insulin iTEM was performed on ultra-thin sections, then morphological markers close to immuno-gold positive structures were correlated to SEM micrographs obtained from the entire resin blockface. Finally, FIB-SEM tomography was performed, resulting in volumes generated from 5-7 nm thin slices. IDeg was visualized in the ECM as long structures measuring ~10 nm in width. FIB-SEM visualization confirmed that, in 3D, these structures connected into long multi-hexamers that distributed into an intricate network of densely packed, yarn-like clusters. In comparison, the morphology of IGlar U300 micro-precipitates in the ECM appeared to consist of amorphous-like structures which, in 2D, appeared heterogeneous in both shape and size. This heterogeneous morphology was confirmed in 3D, as the IGlar U300 micro-precipitates were visualized as both spherical and cylindrical structures with irregular surfaces. In summary, distinct ultrastructural 3D morphologies of IDeg and IGlar have been visualized and are consistent with the different strategies for protraction: micro-precipitation of IGlar in Toujeo, and assembly of IDeg into multi-hexamers for Tresiba.

Supported By: Novo Nordisk Inc.

919-P

Cells Chronically Exposed to the Novel Weekly Insulin HM12470 Are Protected against Desensitization of the Insulin Signaling Cascade

NINA WRONKOWITZ, THORSTEN M. HARTMANN, SVEN W. GÖRGENS, DANIELA DIETZE-SCHROEDER, IN YOUNG CHOI, SUNG HEE PARK, YOUNG MI LEE, SE CHANG KWON, YEONJOO KANG, MARCUS HOMPESCH, JUERGEN ECKEL, *Düsseldorf, Germany, Seoul, Republic of Korea, Chula Vista, CA*

The novel basal insulin HM12470 consists of an insulin analog (Insulin 115) conjugated to the human aglycosylated F_C fragment via a small PEG linker and is developed for once-weekly administration. In the present study, we mimic chronic exposure to HM12470 *in vitro* to analyze the insulin-induced desensitization of target cells. To establish an *in vitro* model of chronic insulin stimulation, human coronary artery smooth muscle cells (hCASMC) were used in light of their high insulin sensitivity and a good tolerance towards long-term treatment. Cells were exposed for 5 days to 500 nM regular insulin (reg. Ins) or HM12470 and allowed to recover for up to 48 h. After 5 days of chronic exposure, insulin receptor (IR) protein abundance was significantly decreased in both HM12470 and reg. Ins treated cells by 42 and 78%, respectively. However, in the HM12470 exposed cells, IR levels recovered completely within 48 h in contrast to reg. Ins. Interestingly, under these conditions IR mRNA levels were not altered, indicating a more efficient translational and/or post-translational recovery of IR in HM12470 treated cells. The most prominent effect was observed at the signaling level, where the insulin stimulated Akt phosphorylation dropped down tremendously in both HM12470 (to 28%) and reg. Ins (to 12%) treated cells. However, total Akt levels were not altered. Insulin signaling in the HM12470 treated cells was almost completely restored after 48 h recovery (72%), whereas the reg. insulin treated cells showed no significant improvement under these conditions. In conclusion, cells chronically exposed to the basal insulin HM12470 showed an improved recovery flexibility of the insulin signaling cascade probably due to changes of IR translation or processing. Thus, HM12470 does not irreversibly desensitize target cells under chronic exposure, and therefore represents an excellent candidate for a weekly insulin.

920-P

Obese T2DM Patients Gain Less Weight with Insulin Treatment Compared with Normal and Overweight Patients: New Evidence from Real-World Data

SANJOY PAUL, JONATHAN SHAW, KERENAFTALI KLEIN, *Brisbane, Australia, Melbourne, Australia*

Barriers to insulin (INS) initiation in obese patients (pts) with T2DM include fear of body weight (BW) gain. In a real-world setting, we evaluated the BW changes over 6, 12 and 24 months (mo) post initiation of INS treatment in relation to baseline BMI and subsequent HbA1c changes.

From the U.S. GE CEMR Database, data were available from INS initiation with INS treatment duration of 6 mo (n=155917), 12 mo (n=151220) and 24 mo (n=144857). Pts receiving GLP-1 RA or SGLT2 during follow-up were excluded.

In the total sample, pts were mean 59 yrs old, HbA1c 9.5%, and BMI 35 kg/m^2 at INS start. The proportions of overweight, Grade 1, 2 and 3 obese pts were 21%, 28%, 21% and 22% respectively. The HbA1c levels at INS start were significantly lower (9.2% to 9.4%) in the obese pts, than in pts with normal BW (10%). However, the proportions of pts with HbA1c > 7.5% or 8% were similar across the BMI categories.

Adjusting for age, sex, other antidiabetes medications, and weighted by baseline BW, the BW gain progressively fell with increasing baseline BMI category over all 3 follow-up periods (Table; p <0.01). Grade 3-obese patients lost BW during follow-up. The adjusted changes in HbA1c over time were similar across BMI categories (Table).

Over 24 mo post initiation of INS, obese pts gained significantly less BW compared to normal and overweight pts, while achieving clinically similar glycemic benefits.

Table. Adjusted Mean Changes in Body Weight and HbA1c by BMI Categories at Insulin Initiation.

BMI Category	Weight Gain (Kg)			HbA1c Change (%)		
	0-6 month	0-12 month	0-24 month	0-6 month	0-12 month	0-24 month
Normal	2.1	3.1	3.9	-1.4	-1.4	-1.4
Over Weight	1.2	1.8	2.0	-1.3	-1.3	-1.3
Grade 1 Obese	0.6	0.9	0.7	-1.2	-1.2	-1.2
Grade 2 Obese	0.2	0.3	-0.2	-1.2	-1.1	-1.2
Grade 3 Obese	-0.7	-1.1	-2.0	-1.1	-1.0	-1.1

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

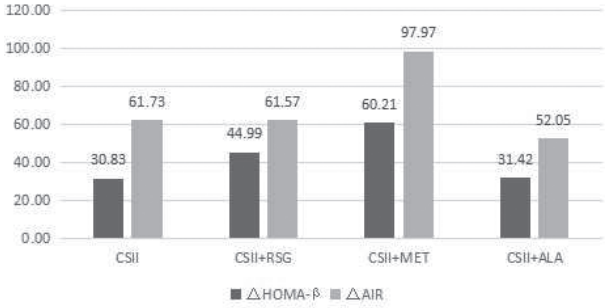
921-P

Determinants of β-cell Function Recovery after Short-Term Insulin Intensive Therapy

XUESI WAN, ZHIMIN HUANG, LIEHUA LIU, WEIJIAN KE, YANBING LI, *Guangzhou, China*

Our previous studies suggest that short-term continuous subcutaneous insulin infusion (CSII) therapy could improve β-cell function in patients with newly diagnosed T2DM. The aim of this study was to identify the determinants. We recruited 160 patients with newly diagnosed T2DM (103 male, aged 49.8±10.4 ys, HbA1c 11±2.1%) underwent 2 weeks of CSII alone or with either rosiglitazone 4 mg QD, or Metformin 500mg TID, or α-lipoic acid 600 mg QD. The HOMA-β and acute insulin response (AIR) during the intravenous glucose tolerance test were performed before and after therapy. After the treatment, HOMA-β and AIR improved markedly. The CSII with Metformin therapy induced more profound increase than other groups ($p<0.05$). Unexpectedly, FPG pro-therapy was positive relative with ΔHOMA-β but negative with ΔAIR. BMI, HSCRP at baseline had strong correlation with both ΔAIR and ΔHOMA-β. The ΔFPG was only associated with ΔHOMA-β. While ΔTG, ΔBMI and ΔHOMA-IR showed positive relation with ΔAIR. The multivariate regression analysis showed BMI and FPG at baseline were independent predictors of ΔHOMA-β (Standardized β=0.35, 0.14 respectively, F=9.46, $p<0.01$). ΔHOMA-IR, BMI and FPG at baseline affected ΔAIR (Standardized β= 0.32, 0.25, -0.30 respectively, F=13.31, $p<0.01$). In conclusion, the recovery of beta cell function is largely determined by baseline condition. And ΔAIR is also affected by the reduction of insulin resistance.

Figure. β-cell Function Recovery after Short-term CSII.



922-P

Sustainable Effects of Basal Insulin Have Favourable Outcomes on Fasting Blood Glucose Level via Increased Insulin/Glucagon Ratio during Fasting in Type 2 Diabetes Patients

SHIZUKA KANEKO, YOUHEI UEDA, YUMIKO TAHARA, NOBUYA INAGAKI, *Takatsuki, Japan, Kyoto, Japan*

We compared insulin degludec therapy (IDeg) which has the longest effect of 42 hours with insulin glargine therapy (IGla) of which the effect is less than 24 hours. Next, we investigated whether transient longer lasting basal insulin therapy has an effect on glucagon and insulin secretion. Three different retrospective studies were conducted. 1.) Comparison of newly introduced IDeg and IGla, 2.) Substitution of IDeg for IGla, 3.) Analysis of insulin/glucagon secretion ratio (I/G ratio) and insulinogenic index (I.I.) after cessation of insulin. 118 patients with insulin naïve T2DM (61 males, 64.2±10.5 years old, disease duration of 7.5±7.4 years, HbA1c 10.6±2.2%, BMI 24.3±4.0) were administered IDeg, and 224 patients with insulin naïve T2DM (95 males, 59.3±12.0 years old, disease duration of 7.2±8.0 years, HbA1c 10.5±3.4%, BMI 25.1±3.9) were administered IGla once-daily. Patients treated with IDeg achieved the target FPG earlier (6.6±3.0 days) than those treated with IGla (9.1±4.7 days) ($p<0.01$). Total doses of IDeg (91.9±65.4 U) needed to achieve the target FPG were less than doses of IGla (116.3±89.7 U) ($p<0.01$). 67 patients undergoing IGla were switched to IDeg for more than 14 days and then switched back to IGla. The average and SD of FPG for 14 days before and after both switch were analyzed. The average and SD of FPG decreased during IDeg in 73.4% and 64.6% of patients, respectively. The amount of insulin was reduced by 10%. Nocturnal hypoglycemia occurred in 1% and 5% of patients undergoing IDeg and IGla, respectively. Measurements taken prior to therapy and after cessation of therapy show that IDeg induces an increase in I/G ratio during fasting and I.I. ($P<0.01$). Our study suggests longer active basal insulin therapy provides more success in diabetic therapy regarding effectiveness and safety. In addition, IDeg might also lead to reduced medical cost due to a decrease in and insulin dosage and hypoglycemic events.

Supported By: Japan Vascular Disease Research Foundation

923-P

Titration and Optimization (TOP) Trial for Insulin Glargine U100 (Gla-100) in Type 2 Diabetes (T2DM) Patients (pts) Poorly Controlled on Oral Antidiabetic Drugs

JOCHEN SEUFERT, ANDREAS FRITSCHE, STEFAN PSCHERER, HELMUT ANDERTEN, KATRIN PEGELOW, MARTIN PFOHL, *Freiburg, Germany, Tübingen, Germany, Weimar, Germany, Hildesheim, Germany, Berlin, Germany, Duisburg, Germany*

Adding Gla-100 improves glycemic control in pts poorly controlled on OADs, but titration algorithms differ in daily clinical practice. This is a prospective (12 months), observational study in T2DM pts in German GP offices to assess efficacy of different Gla-100 titration algorithms. Physicians enrolled pts on OADs ± basal insulin other than Gla-100 with an A1c of 7.5-10%, and indicated before enrollment, whether they will use a titration algorithm according to Fritsche (F; Ann Intern Med. 2003), Davies (D; Diabetes Care 2005) or individual titration (IT), leading to preassigned strata of Gla-100 titration. Co-primary endpoint was defined as achieving a FBG ≤110 mg/dL or an individual A1c target. In Nov 2015, 2,477 pts were assigned to F (46%), D (29%) or IT (22%). Pts baseline demographic data were similar despite more concomitant OADs (≥3 drugs; p=0.0003) and sulphonylurea (p=0.002) in IT. After 12 months 86.1% (F), 86.9% (D) and 82.8% (IT; p=0.10) continued to receive Gla-100. Insulin doses were lower in D (21.4 U/d) compared to F and IT (both 23.1 U/d; p=0.0017). More OADs were given in IT (≥3 drugs; p=0.02). Outcomes were similar for A1c (F 7.1%, D 7.2%, IT 7.2%; p=0.27); mean A1c 7.2±0.9%. FBG was different (F 127 mg/dL, D 122 mg/dL, and IT 127 mg/dL; p=0.0012); mean FBG was 125.2±28.9 mg/dL. Target achievement was significantly different for FBG (D 41.5% vs. F 36.2% and IT 35.0%; both p=0.03), but not for A1c (F 49.9%, D 47.7%, IT 52.6%; p=0.26) and the co-primary endpoint (F 64.1%, D 64.7%, IT 65.7%; p=0.81). Confirmed symptomatic (0.04 events/pt year [E/pty; 95% CI 0.03-0.05 E/pty)], nocturnal (0.01 E/pty [95% CI 0.01-0.02 E/pty)] or severe hypoglycemia event rates (0.0 E/pty [95% CI 0.0-0.0 E/pty)] were low and not significantly different between groups. The investigated Gla-100 titration algorithms yielded similar A1c target attainment, but not FBG target attainment in T2DM pts, leading to 65% of pts achieving the co-primary endpoint.

Supported By: Sanofi-Aventis Deutschland GmbH

924-P

WITHDRAWN

925-P

IDegLira Is Efficacious across Baseline A1c Categories in Subjects with Type 2 Diabetes Uncontrolled on SU, GLP-1RA, or Insulin Glargine: Analyses from Completed Phase 3b Trials

CHRISTOPHER H. SORLI, STEWART B. HARRIS, ESTEBAN JÓDAR, ILDIKO LINGVAY, KEVAL CHANDARANA, JAKOB LANGER, ELMAR JAECKEL, *Billings, MT, London, ON, Canada, Madrid, Spain, Dallas, TX, Søborg, Denmark, Hannover, Germany*

Previous analyses of phase 3a trials (DUAL I extension; DUAL II) showed insulin degludec/liraglutide (IDegLira) is efficacious irrespective of baseline A1c. This *post hoc* analysis aimed to confirm this observation in additional populations with type 2 diabetes uncontrolled on (i) a glucagon-like peptide-1 receptor agonist (GLP-1RA) (DUAL III: IDegLira vs. unchanged GLP-1RA), (ii) sulfonylurea (SU) ± Metformin (DUAL IV: IDegLira vs. placebo) or (iii) insulin glargine (IGlar) (DUAL V: IDegLira vs. continued IGlar titration). IDegLira starting dose was 10 dose steps (1 dose step = 1 U IDeg + 0.036 mg Lira) in DUAL IV and 16 dose steps in DUAL III and V; maximum IDegLira dose: 50 dose steps. Subjects were grouped according to baseline A1c; ≤7.5, >7.5-≤8.5 and >8.5%. In all trials a higher baseline A1c resulted in greater A1c reductions. The change in A1c was significantly greater with IDegLira vs. comparator in all baseline A1c groups with a similar treatment difference between baseline A1c groups. In all trials for all baseline A1c groups, IDegLira decreased mean A1c to <7% at end of trial. In DUAL V, the only trial to include patients with A1c >9% (mean 9.6%), A1c was reduced to 6.9% with IDegLira vs. 7.8% with IGlar. In conclusion, significant A1c reductions occur with IDegLira regardless of baseline A1c group or study population.

Table. Change in A1c by Baseline A1c Category in DUAL III, IV and V.

		Overall	Baseline A1C ≤7.5%	Baseline A1C >7.5%–≤8.5%	Baseline A1C >8.5%
DUAL III	**IDegLira, N**	**292**	**113**	**141**	**38**
	Baseline A1C,% (±SD)	7.8 (±0.6)	7.2 (±0.2)	8.0 (±0.3)	8.8 (±0.2)
	ΔA1C, % (±SD)	-1.3 (±0.8)	-1.0 (±0.7)	-1.4 (±0.8)	-1.9 (±1.2)
	GLP-1RA, N	**146**	**66**	**66**	**14**
	Baseline A1C,% (±SD)	7.7 (±0.6)	7.2 (±0.2)	8.0 (±0.3)	8.9 (±0.3)
	ΔA1C, % (±SD)	-0.3 (±0.9)	-0.3 (±0.8)	-0.3 (±1.0)	-1.0 (±1.2)
	ETD [95% CI]*	-0.94 [-1.11;-0.78]	-0.74 [-0.95;-0.52]	-1.13 [-1.38;-0.88]	-1.18 [-1.95; -0.40]
	***p* value**	p<0.001	p<0.001	p<0.001	p=0.004
DUAL IV	**IDegLira, N**	**289**	**93**	**156**	**40**
	Baseline A1C,% (±SD)	7.9 (±0.6)	7.2 (±0.3)	8.0 (±0.3)	8.8 (±0.2)
	ΔA1C, % (±SD)	-1.5 (±0.8)	-1.0 (±0.6)	-1.5 (±0.9)	-2.1 (±0.9)
	Placebo, N	**146**	**48**	**80**	**18**
	Baseline A1C,% (±SD)	7.9 (±0.6)	7.2 (±0.3)	8.1 (±0.3)	8.8 (±0.2)
	ΔA1C, % (±SD)	-0.5 (±0.8)	-0.2 (±0.7)	-0.6 (±0.9)	-0.7 (±0.9)
	ETD [95% CI]*	-1.02 [-1.18;-0.87]	-0.91 [-1.11; -0.72]	-1.00 [-1.23; -0.76]	-1.36 [-1.88; -0.84]
	***p* value**	p<0.001	p<0.001	p<0.001	p<0.001
DUAL V	**IDegLira, N**	**278**	**63**	**102**	**113**
	Baseline A1C,% (±SD)	8.4 (±0.9)	7.2 (±0.2)	8.1 (±0.3)	9.3 (±0.6)
	ΔA1C, % (±SD)	-1.8 (±1.1)	-1.0 (±0.6)	-1.6 (±1.0)	-2.5 (±1.0)
	IGlar, N	**279**	**64**	**118**	**97**
	Baseline A1C,% (±SD)	8.2 (±0.9)	7.1 (±0.3)	8.1 (±0.3)	9.2 (±0.5)
	ΔA1C, % (±SD)	-1.1 (±1.0)	-0.5 (±0.8)	-1.0 (±0.9)	-1.7 (±0.9)
	ETD [95% CI]†	-0.59 [-0.74;-0.45]	-0.48 [-0.73; -0.23]	-0.55 [-0.80; -0.31]	-0.68 [-0.93; -0.42]
	***p* value**	p<0.001	p<0.001	p<0.001	p<0.001

Based on the full analysis set. Missing data is imputed using last observation carried forward. *Analyzed using ANCOVA with treatment, previous antidiabetic therapy and region as fixed factors and baseline A1C as covariate. †Analyzed using ANCOVA with treatment and region as fixed effects and baseline A1C as covariate. A1C, glycated hemoglobin; ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; N, number of subjects; SD, standard deviation

Supported By: Novo Nordisk Inc.

Moderated Poster Discussion: What You Want to Know about Insulin Therapy and Maybe Need to Ask *(Posters: 926-P to 933-P), see page 17.*

926-P

Efficacy and Safety of MK-1293 Insulin Glargine Compared with Originator Insulin Glargine (Lantus) in Type 2 Diabetes (T2D)

PRISCILLA HOLLANDER, GREGORY GOLM, WENDY CAROFANO, ROY ELDOR, MICHAEL CRUTCHLOW, MICHAEL MARCOS, MARC RENDELL, PHILIP HOME, BAPTIST GALLWITZ, JULIO ROSENSTOCK, *Dallas, TX, Kenilworth, NJ, Omaha, NE, Newcastle, United Kingdom, Tübingen, Germany*

MK-1293 is a biosimilar insulin glargine under development using Lantus as the originator benchmark. This phase 3, randomized, active-controlled, open-label 24-week trial enrolled 531 people with T2D (A1c ≤11.0%) eligible for or taking basal insulin (≥10 U/day). Participants were randomized 1:1 to once daily MK-1293 (n=265) or Lantus (n=266) guided by a fasting glucose-based dosing algorithm. Oral agents and prandial insulin were to be continued. The primary efficacy objective was non-inferiority of change from baseline A1c (margin of 0.40%) MK-1293 vs. Lantus at week 24. The primary safety objective was anti-insulin antibody (AIA) development at week 24. The LS mean A1c difference (MK-1293 minus Lantus) was 0.03 (95% CI: -0.12, 0.18)%, meeting non-inferiority and equivalence (secondary objective) criteria. Insulin doses were similar between groups (Table). Similar AIA responses, including incidence (Table) and titers, and similar neutralizing antibody responses were seen between treatment groups. No clinically meaningful between-group differences were seen for pre-defined safety endpoints of interest (Table). The efficacy and safety of MK-1293 and Lantus were similar in people who were insulin treated at baseline (n=185 [~70%] in both treatment groups) and those who were not. In summary, MK-1293 demonstrated similar efficacy and safety to Lantus in T2D over 24 weeks.

Table.

	MK-1293	Lantus	Difference[c] (95% CI)
Efficacy endpoints (at week 24)			
A1c change from baseline (%)[a]	-1.28 (-1.41, -1.15)	-1.30 (-1.43, -1.18)	0.03 (-0.12, 0.18)
Basal insulin dose (U/day)[b]	48.3 (45.0, 51.6)	46.8 (43.5, 50.1)	1.5 (-2.1, 5.1)
FPG change from baseline (mg/dL)[a]	-35.0 (-41.3, -28.6)	-38.5 (-44.8, -32.1)	3.5 (-3.7, 10.7)
Anti-insulin antibodies (n/N (%) participants)			
AIA positive at or before week 24			
Irrespective of AIA status at baseline	91/262 (34.7%)	76/261 (29.1%)	5.6 (-2.4, 13.6)
Participants AIA negative at baseline	37/192 (19.3%)	29/196 (14.8%)	4.5 (-3.0, 12.1)
Safety endpoints of interest (n/N (%) participants)			
Symptomatic hypoglycemia	140/263 (53.2%)	137/263 (52.1%)	1.1 (-7.4, 9.6)
Injection site reaction	5/263 (1.9%)	1/263 (0.4%)	1.5 (-0.4, 4.0)
Systemic allergic reaction	1/263 (0.4%)[d]	0	–
Anaphylactic response	1/263 (0.4%)[e]	0	–
Angioedema (narrow definition), or severe cutaneous adverse reaction (broad definition)	1/263 (0.4%)	2/263 (0.8%)	–

[a]Expressed as LS mean change from baseline (95% CI). [b]Expressed as LS mean (95% CI). [c]MK-1293 minus Lantus (LS means for efficacy endpoints; % people for safety endpoints). [d]The systemic allergic reaction was allergic dermatitis, non-serious and attributed to a concomitant medication. [e]The anaphylaxis event was 9 days after last study medication, and attributed to concomitant medication. A1c= glycated hemoglobin; CI= confidence interval; FPG=fasting plasma glucose; LS= least-squares.

Supported By: Merck & Co., Inc.

927-P

Short-Term Intensive Insulin Therapy did Not Significantly Change Fasting Serum Glucagon Level in Patients with Newly Diagnosed Type 2 Diabetes

LIEHUA LIU, WEIJIAN KE, PENGYUAN ZHANG, JUAN LIU, HAI LI, HAI LI, WANPING DENG, YANBING LI, YANBING LI, *Guangzhou, China*

Short-term intensive insulin therapy (ITT) can induce glycemic remission by improving insulin sensitivity and restoring β-cell function. However, it is uncertain whether circulating glucagon level is modified by the treatment.

Thirty patients with newly diagnosed type 2 diabetes mellitus (T2DM) were treated with short-term ITT using insulin pump. Near-normoglycemia (FBG 4.4-6.1mmol/L, PBG 4.4-7.8mmol/L) was achieved and maintained for 2 weeks by insulin dose adjustment according to daily 8-point capillary blood glucose monitoring (before and 2 hours after 3 meals, 11pm and 3am). Intravenous glucose tolerance tests were performed before and after the therapy, with HOMA IR, HOMA B and acute insulin response (AIR) calculated. Fasting plasma glucose (FPG), 2 h post-breakfast plasma glucose (PPG) and fasting serum glucagon (Gcg) levels were measured before and after ITT.

FPG (11.1±3.2 vs. 6.6±1.1mmol/L, P<0.001) and PPG (16.4±5.6 vs. 8.82±2.2 mmol/L) were significantly decreased after ITT. Both HOMA B and AIR were significantly elevated while HOMA-IR was decreased after ITT. Fasting Gcg were 48.5±19.1pg/ml at baseline and 50.4±20.4 pg/ml after the therapy (P>0.05). After ITT, fasting Gcg was not significantly correlated with either FPG (r=-0.19, P=0.30) or PPG (r=-0.20, P=0.27). Change of fasting Gcg from baseline was weakly correlated with decrement of HOMA IR (r=-0.43, P=0.02), but not with HOMA B (r=0.15, P=0.43) or AIR (r=-0.10, P=0.58) after the therapy. The patients who achieve glycemic remission after stop of ITT had similar fasting Gcg level with the non-remission patients (48.5±21.8 vs. 53.7±18.2pg/ml, P=0.50).

Fasting serum Gcg level was not significantly changed by short-term ITT in patients with newly diagnosed T2DM. Thus, alleviation of α cell dysfunction may not be a major mechanism for glycemic remission induced by short-term ITT in these patients.

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For author disclosure information, see page A696.

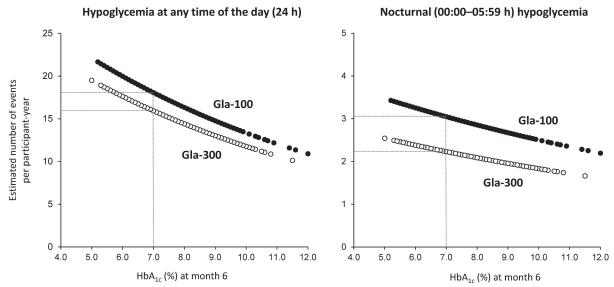
928-P

Hypoglycemia as a Function of HbA1c in Type 2 Diabetes (T2DM): Insulin Glargine 300 U/mL in a Patient-Level Meta-analysis of EDITION 1, 2, and 3

RICCARDO C. BONADONNA, JEAN-FRANÇOIS YALE, CLAIRE BRULLE-WOHLHUETER, EMMANUELLE BOËLLE-LE CORFEC, PRATIK CHOUDHARY, TIMOTHY S. BAILEY, *Parma, Italy, Montreal, QC, Canada, Paris, France, Chilly Mazarin, France, London, United Kingdom, Escondido, CA*

Basal insulin therapy can be a compromise between achieving glycemic targets and avoiding hypoglycemia, dependent on how intensively insulin is titrated. In the phase 3a EDITION 1, 2 and 3 studies, insulin glargine 300 U/mL (Gla-300) provided equivalent glycemic control to insulin glargine 100 U/mL (Gla-100) with less hypoglycemia in people with T2DM. The objective of the current analysis was to evaluate rates of confirmed (≤70 mg/dL) or severe hypoglycemia over 6 months of treatment with Gla-300 or Gla-100 in these EDITION studies, as a function of HbA_{1c}. Meta-analysis was performed on patient-level data, and annualized hypoglycemia rate as a function of HbA_{1c} at month 6 was fitted using a negative binomial regression model. Adding a treatment-by-HbA_{1c} interaction term to the model did not significantly improve the goodness of fit (interaction p-value 0.937 and 0.829 for anytime [24 h] and nocturnal [00:00-05:59 h] hypoglycemia, respectively). Therefore the model without interaction describes the data accurately: people treated with Gla-300 experienced a consistently lower rate of confirmed (≤70 mg/dL) or severe hypoglycemia vs. those treated with Gla-100, regardless of HbA_{1c} at month 6 (Figure). In conclusion, these results suggest that treatment with Gla-300 vs. Gla-100 could allow people with T2DM to achieve equivalent glycemic control with less hypoglycaemia.

Figure. Estimated Annualized Rates of Confirmed (≤70 mg/dL) or Severe Hypoglycemia Over 6 Months of Treatment with Gla-300 or Gla-100 in the EDITION 1, 2 and 3 Studies as a Function of HbA_{1c} at Month 6.



Supported By: Sanofi (NCT01499082, NCT01499095, NCT01676220)

929-P

Faster Onset and Greater Early Exposure and Glucose-Lowering Effect with Faster-Acting Insulin Aspart vs. Insulin Aspart: A Pooled Analysis in Subjects with Type 1 Diabetes

TIM HEISE, THOMAS R. PIEBER, THOMAS DANNE, LARS ERICHSEN, HANNE HAAHR, *Neuss, Germany, Graz, Austria, Hannover, Germany, Søborg, Denmark*

Faster-acting insulin aspart (faster aspart) is insulin aspart (IAsp) set in a new formulation with added excipients and faster initial absorption after subcutaneous (s.c.) injection. This pooled analysis of PK/PD properties of faster aspart vs. IAsp included 218 adult subjects with type 1 diabetes from 6 phase 1 randomized, double-blind, crossover trials. Subjects received single s.c. doses (0.2 U/kg) of faster aspart and IAsp. In 3 trials, a 12-hour automated euglycemic clamp was performed (target 100 mg/dL). Onset of appearance was twice as fast (~5 min earlier; Table) and $t50\%C_{max}$ was 9.5 min earlier with faster aspart than IAsp, resulting in two-fold higher insulin exposure during the first 30 min and higher insulin exposure up to 2 hrs after injection with faster aspart than IAsp. The higher early exposure of faster aspart translated into a left shift of the glucose-lowering effect profile. Onset of action was 23% faster, $t50\%GIR_{max}$ was 21% earlier and the glucose-lowering effect during the first 30 min was 74% greater with faster aspart than IAsp. Total exposure, maximum concentration and total and maximum glucose-lowering effect were similar between treatments. In conclusion, in a pooled analysis faster aspart demonstrated faster onset and higher early insulin exposure that led to greater early glucose-lowering effect vs. IAsp.

Table. Pharmacokinetic and Pharmacodynamic Results for Faster Aspart vs. IAsp.

PK endpoints (insulin exposure[a])	N=261/256[b]	PD endpoints (glucose-lowering effect)	N=163/160[b]
Onset	**Treatment difference Faster aspart-IAsp [95% CI] (minutes)**	**Onset**	**Treatment difference Faster aspart-IAsp [95% CI] (minutes)**
Onset of appearance $t50\%C_{max}$	-4.9 [-5.3;-4.4] -9.5 [-10.7;-8.3]	Onset of action $t50\%GIR_{max}$	-4.9 [-6.9;-3.0] -9.5 [-12.5;-6.4]
Early exposure	**Treatment ratio Faster aspart/IAsp [95% CI]**	**Early effect**	**Treatment ratio Faster aspart/IAsp [95% CI]**
$AUC_{0\text{-}15min}$ $AUC_{0\text{-}30min}$ $AUC_{0\text{-}1h}$ $AUC_{0\text{-}2h}$	3.83 [3.41;4.29] 2.01 [1.87;2.17] 1.32 [1.26;1.39] 1.10 [1.06;1.14]	– $AUC_{GIR,\ 0\text{-}30min}$ $AUC_{GIR,\ 0\text{-}1h}$ $AUC_{GIR,\ 0\text{-}2h}$	– 1.74 [1.47;2.10][c] 1.34 [1.25;1.43] 1.13 [1.07;1.19]
Total exposure	**Treatment ratio Faster aspart/IAsp [95% CI]**	**Total effect**	**Treatment ratio Faster aspart/IAsp [95% CI]**
$AUC_{0\text{-}12h}$ C_{max}	1.01 [0.98;1.04] 1.04 [1.00;1.08]	$AUC_{GIR,\ 0\text{-}12h}$ GIR_{max}	0.98 [0.94;1.03] 1.01 [0.96;1.05]

[a] Based on free serum insulin aspart; [b] N is number of profiles contributing to the analysis for faster aspart/IAsp; [c] Treatment ratio and 95% CI estimated using Fieller's method. AUC, area under the curve; CI, confidence interval; C_{max}, maximum observed concentration; Faster aspart, faster-acting insulin aspart; GIR_{max}, maximum glucose infusion rate; IAsp, insulin aspart; Onset of appearance, time from dosing until the first time serum IAsp concentration ≥ lower limit of quantification; PK, pharmacokinetic; PD, pharmacodynamic; $t50\%C_{max}$, time to 50% of maximum serum insulin aspart concentration; $t50\%GIR_{max}$, time to 50% of maximum glucose infusion rate.

(NCT01618188), (NCT01924637), (NCT02003677), (NCT02033239), (NCT02035371), and (NCT02131246).

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930-P

WITHDRAWN

931-P

Technosphere® Inhaled Human Insulin Has a More Rapid Onset of Action Than Subcutaneous Insulins: Meta-analysis of Clamp Data from Three Clinical Studies

YOUSSEF HIJAZI, ANDERS BOSS, THOMAS KLABUNDE, RAPHAEL DAHMEN, DIETHER RUEPPEL, ROBERT A. BAUGHMAN, *Frankfurt, Germany, Bridgewater, NJ, Danbury, CT*

Technosphere® Inhaled (TI) human insulin is characterized by fast absorption and short half-life. Based on a single, small 12-patient study (NCT01544881), it was previously reported that TI insulin has similar onset of action as subcutaneously (sc) applied Insulin Lispro despite its faster absorption (Nuffer W. et al, Ann Pharmacother. 2015). The aim of this analysis was to verify whether pharmacokinetic (PK) properties of TI insulin translate into a faster onset of action compared to sc regimens.

Pooled data from 3 euglycemic clamp studies (NCT01490762: 32 healthy volunteers, NCT01544881: 12 type 1 diabetics, NCT0062857: 25 type 1 diabetics) were analyzed using WinNonlin Phoenix® software. Area under glu-

cose infusion rate (GIR) from time 0 till 240 min ($GIR_{AUC0-240}$) and time (T) to reach partial areas (10 and 50% $GIR_{AUC0-240}$) were estimated using the linear trapezoidal rule. GIR profiles were fitted to first order input and first order output mathematical models to estimate time to maximum GIR (T-GIR_{max}) and time to 20 and 50% GIR_{max}.

This pooled analysis—using a larger sample size than the earlier analysis based on a single study—demonstrated faster onset of action for TI insulin than sc insulins based on all GIR_{max} and $GIR_{AUC0-240}$ parameters (Table 1). These findings can be relevant for optimal dosing of TI insulin with respect to meals.

Table 1. Onset of Action Parameters of TI Insulin vs. SC Insulin Based on Pooled Analysis from 3 Clinical Studies (Range Across Studies).

Dosage form	T- GIR_{max} (min)	T-20% GIR_{max} (min)	T-50% GIR_{max} (min)	T-10% $GIR_{AUC0-240}$ (min)	T-50% $GIR_{AUC0-240}$ (min)	Insulin T_{max} (min)
TI insulin	37-57	2.5-18	7.7-16	25-34	75-112	7.5-15
SC insulin	110-183	13-34	40-47	53-60	132-143	50-120

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932-P

Attenuated Suppression of Lipolysis by Basal Insulin Peglispro (BIL) May Increase Triglyceride (TG) Secretion and Concentration Compared with Insulin Glargine (GL) in Patients with Type 1 Diabetes (T1D)

RAKEL F. JOHANSEN, ESBEN SØNDERGAARD, NIELS PORKSEN, HELLE LINNEBJERG, PARAG GARHYAN, ERIC CHEN QUIN LAM, SØREN NIELSEN, *Aarhus, Denmark, Indianapolis, IN, Singapore, Singapore*

BIL is a novel PEGylated basal insulin with a flat pharmacokinetic and glucodynamic (GD) profile and a hepato-preferential action resulting from reduced peripheral effects on glucose. In Phase 3 trials in patients with T1D, BIL increased plasma TG and hepatic fat relative to baseline and GL, while lowering weight. Insulins potently inhibit lipolysis and hepatic very low-density lipoprotein (VLDL)-TG secretion, stimulate lipogenesis, and cause weight gain. We hypothesized that BIL, compared to GL, due to attenuated peripheral insulin action, would increase lipolysis, VLDL-TG secretion, and oxidation, with reduced lipogenesis. This open-label, randomized, 2-period crossover study investigated the effects of BIL on whole body lipid metabolism. Fourteen patients (mean ± SD age, 35.3 ± 15.3 yrs; duration of T1D, 13.5 ± 14.5 yrs) received once-daily, individualized, stable doses of BIL or GL for 3 weeks. Palmitate flux was measured via a 1-h [9,10-^{3}H] palmitate infusion followed by a 420-min primed constant infusion of ex vivo labeled [1-^{14}C]triolein VLDL-TG and a bolus injection of [9,10-^{3}H] triolein VLDL-TG, with blood, breath, and fat biopsy sampling to assess VLDL-TG secretion, oxidation, clearance, and fat tissue storage rates. Mean VLDL-TG concentration and secretion rate, and palmitate flux were significantly higher with BIL than GL (58%, 51%, and 35%, respectively). Mean VLDL-TG clearance, oxidation, and storage rates were not different for BIL vs. GL (ratio [difference for storage rate] of LS geometric means [90% CI] of 0.92 [0.75, 1.12], 1.31 [0.97, 1.78], and -0.36 [-0.75, 0.04], respectively). Glucose was stable during the 2 treatment periods. BIL increased lipolysis, VLDL secretion, and plasma TG vs. GL, explaining the increased plasma TG seen in Phase 3 trials. The data support attenuated effects of BIL on lipolysis, in addition to the known hepato-preferential GD effects.

Supported By: Eli Lilly and Company

933-P

Pharmacokinetic and Pharmacodynamic Profiles of Orally, Duodenally, and Subcutaneously Delivered Insulin in Beagle Canines

YA-ZHUO LI, WEI-DANG WU, RONG ZENG, YAEL GREENBERG-SHUSHLAV, MIRIAM KIDRON, *Tianjin, China, Kfar Haoranim, Israel, Jerusalem, Israel*

Due to its direct delivery to the hepatic portal system, orally delivered insulin harbors the potential to better mimic physiologically secreted insulin, when compared to subcutaneously delivered insulin. For this same reason, it is projected to have a more favorable impact on hypoglycemia incidence. However, its gastrointestinal absorption is hampered by numerous endogenous enzymatic and mechanical barriers. In order to assess the pharmacokinetic profile and pharmacodynamic effect of an oral insulin formulation (ORMD-0801; 8 mg insulin), insulin was delivered per os in capsule form (PO), directly to the duodenum (DU), or subcutaneously (SC; 5 U/dog), to four fasting beagle canines. Plasma insulin, glucose and c-peptide concentrations were determined over the ensuing 6 h, and exogenous insulin concentrations were extrapolated. Maximum exogenous insulin concentrations were highest for PO insulin (625±360 U), followed by DU (453±436 U) and SC (101±45.7 U) insulin. Peak absorption was reached within a mean 0.75±0.29 h and 0.5±0.6 h in the PO and DU sessions, respectively, and by 0.38±0.22 h for the SC insulin. Mean exogenous insulin area under the curve was similar between the two PO and DU sessions (414±246 µU/ml*h and 423±526 µU/ml*h, respectively), and significantly higher than after SC delivery (181±42.6 µU/ml*h). Relative bioavailability of PO insulin and DU insulin was 5.4±2.3% and 8.3±9.9%, respectively. Of note, high inter-animal variability in absorption of exogenous insulin was observed. Onset of action was typically immediate for the DU and SC insulins and with a lag of 15 min for the PO insulin. Overall effects on plasma glucose concentrations were similar across delivery modes and was maximal 1-1.5 h after oral dosing and returned to baseline within 4 h of dosing. These findings demonstrate the feasibility of oral delivery of insulin, which was characterized by a rapid onset and short duration of action, similar to those observed for SC insulin.

934-P

Prevalence of Timely (TI), Delayed (DI) and No Intensification (NI) of T2D Treatment and Predictors of TI in T2D Patients Uncontrolled on Basal Insulin (BI)

PHILIP LEVIN, STEVE ZHOU, TAO FAN, XUE SONG, DAMION NERO, BRIAN DAVIS, BONG-CHUL CHU, *Baltimore, MD, Bridgewater, NJ, Ann Arbor, MI*

Currently, data on clinical inertia, including DI and NI, in T2D pts uncontrolled after failure to control A1c with basal insulin is scarce.

This retrospective study of 17,316 T2D pts uncontrolled on BI after ≥6 months used data from U.S. national claims databases between January 2005 and December 2014. Date of first uncontrolled A1c was the index date (HEDIS criteria: A1c ≥8% if age ≥65 or evidence of a comorbid condition; else A1c ≥7). Pts were stratified into: receiving timely intensification (Int: date of intensification: receiving add-on therapies) ≤6 months after index date (TI); receiving Int > 6 months (DI); not receiving Int (NI). Pre-period (6 months prior to Int) demographics and clinical characteristics were investigated to determine predictors of TI.

During follow up, 46.4% of pts had TI, 13.1% DI and 40.5% had NI. Pts over 75 years, with >1 baseline OADs and with Deyo-Charlson Comorbidity Index 2-4 were less likely to have TI. Pts in U.S. region North-east and -central, with A1c value ≥8%, being overweight or obese, having hypoglycemia, sleep apnea, endocrinologist visits, and several concomitant medications were more likely to have TI (Table).

DI and NI are common in T2D pts uncontrolled on BI and pose a challenge for control of T2D. The predictors identified provide potential insights to better direct efforts aimed at reducing DI and NI in this pt population.

Table. Treatment Intensification within 6-Months of Poor Glycemic Control (N=8,034) Compared to No Treatment Intensification Within 6-Months of Poor Glycemic Control (Intensification >6-Months or No Intensification During the Study Period; N=9,282).

	Odds ratio	95% CI	*P* value
Age ≥ 75 years	0.80	0.64, 0.98	0.034
Region			
U.S. region north-east	1.17	1.05, 1.30	0.004
U.S. region north-central	1.16	1.04, 1.30	0.010
U.S. region West	0.96	0.88, 1.06	0.462
2-4 adjusted DCI	0.88	0.80, 0.98	0.014
A1c			
A1c value 8% to 9%	1.64	1.49, 1.81	<0.001
A1c value ≥ 9%	2.09	1.90, 2.29	<0.001
OADs			
1 OAD medication	0.83	0.73, 0.93	0.002
2 OAD medications	0.72	0.65, 0.81	<0.001
≥3 OAD medications	0.66	0.61, 0.72	<0.001
Concomitant medications			
Aldosterone antagonist	1.36	1.10, 1.67	0.004
Beta blocker	1.14	1.06, 1.23	<0.001
Diuretic	1.14	1.05, 1.23	0.001
Overweight/Obesity*	1.12	1.02, 1.24	0.017
Hypoglycemia	1.14	1.01, 1.29	0.039
Sleep apnea	1.24	1.08, 1.43	0.002
Endocrinologist visit	1.35	1.21, 1.49	<0.001

Reference groups: ≤40 years old; U.S. region south; <1 Deyo-Charlson Comorbidity Index (DCI); zero oral antidiabetic (OAD) medication. *Overweight or obese was captured from ICD-9-CM diagnosis codes (278.0x; V85.2x-V85.4x).

Supported By: Sanofi U.S.

For author disclosure information, see page A696.

935-P

Recovery of Different Insulin Analogs in Different Insulin ELISAs Is Dependent on pH and Assay Specificity

CORINTH A. AULD, XENIA STEINHARDT, CAROLINA GÄREDAL, ANNIKA CARLSSON, SARA HEDLUND, HANNA RITZÉN, *Winston-Salem, NC, Uppsala, Sweden*

Insulin analogs can be used in the treatment of type 1 and type 2 diabetes. Their molecular structures differ from that of insulin and thus different recoveries are observed in diagnostic assays (e.g., ELISA). The contribution of analogs to total insulin measurement is an important issue for patient samples. Therefore, the aim of this study was to determine the cross-reactivity and interference of insulin analogs in 3 different insulin ELISAs in order to evaluate their specificity.

The study was performed with three different commercially available assays; one with a normal dynamic range, one measuring in the ultrasensitive range and one assay with broad specificity (Iso-Insulin ELISA). Each analog was analyzed in pH 4.4 and 7 to observe the effect of solubility on recovery. Dilution series of the insulin analogs were made, covering their range of plasma concentrations, and the interference was investigated by spiking with the highest concentrated calibrator.

Cross-reactivity of the insulin analogs varied in the different ELISAs. Glargine and M1 cross-reacted as much as 30% with the normal range and Ultrasensitive Insulin ELISA. Aspart and M2 showed low cross-reactivity (up to 8%) in both assays. Glulisine, Lispro, Detemir and Degludec showed no cross-reactivity in either insulin assay. However, Lispro, Detemir and Degludec exhibited 100% cross-reactivity in the Iso-Insulin ELISA. The other insulin analogs also had high cross-reactivity in the Iso-Insulin ELISA. Different recoveries were observed in pH 4.4 and 7. Glargine, M1 and M2 had higher recoveries in pH 4.4, whereas Degludec and Detemir had higher recoveries in pH 7.

We conclude that there are different cross-reactivities of insulin analogs in various insulin ELISAs and that pH plays a role in the recovery of analogs depending on their solubility. The results for Lispro, Detemir, Degludec and Glargine present an opportunity to combine assays for the specific measurement of insulin analogs and human insulin in the same sample.

936-P

Double Dose (DD) of Basal Insulin Peglispro (BIL) vs. Glargine (GL) Results in Markedly Lower Incidence of Hypoglycemia in Patients with T2D: IMAGINE 8

CYNTHIA J. HARRIS, THOMAS FORST, TIM HEISE, LEONA PLUM-MÖRSCHEL, ELAINE WATKINS, LUDI FAN, PARAG GARHYAN, NIELS K. PORKSEN, *Indianapolis, IN, Mainz, Germany, Neuss, Germany, Chula Vista, CA*

BIL is distinguished from existing basal insulins by a peripheral-to-hepatic distribution more like endogenous insulin. BIL has a prolonged duration of action with a flat PK/PD profile at steady state. These characteristics should help minimize hypoglycemia risk vs. GL even in settings like dosing errors leading to a DD administration.

In this Phase 3, randomized (N=68), double-blind, 2 period, cross-over study, patients with T2D previously treated with insulin received an individualized, stable dose of BIL or GL once nightly for 3 weeks/period. A single DD was given after 2 weeks, during a 7-day inpatient stay with hourly BG monitoring and standardized meals. Glucose infusion was provided if BG was <54 mg/dL or for symptoms of neuroglycopenia.

The day before DD, mean±SE BG was 161±3.4 mg/dL for BIL and 152±3.4 mg/dL for GL and fewer patients experienced BG ≤70 mg/dL with BIL than GL. During the 4 days after DD, significantly fewer patients experienced BG <54 mg/dL on BIL compared to GL (Table). Similarly, fewer patients experienced BG ≤70 mg/dL with DD BIL and spent less time with BG ≤70 mg/dL than with DD GL (BIL: 95 min; GL: 362 min; p<0.001). ALT increased with BIL (2.7±1.1 U/L) but decreased with GL (-2.8±1.1 U/L; p<0.001).

In conclusion, BIL has a markedly lower risk of hypoglycemia than GL when replicating a DD dosing error in T2D.

Table. Incidence of Hypoglycemia During Inpatient Visit.

Incidence, n (%)	GL (N=62)	BIL (N=61)	OR (95% CI)	p-value[a]
Significant Hypo (BG <54 mg/dL)				
84 hours after DD	22 (35.5%)	4 (6.6%)	0.13 (0.04, 0.39)[b]	<0.001
First 12 hours after DD	14 (22.6%)	1 (1.6%)	Cannot Estimate	0.002[c]
Total Hypo (BG ≤70 mg/dL)				
84 hours after DD	51 (82.3%)	26 (42.6%)	0.15 (0.08, 0.31)	<0.001
First 12 hours after DD	40 (64.5%)	12 (19.7%)	0.12 (0.05, 0.27)	<0.001
Before receiving DD	25 (39.7%)	3 (4.8%)	0.08 (0.02, 0.24)	<0.001

Abbreviations: BG=blood glucose; BIL=basal insulin peglispro; GL=glargine; Hypo=hypoglycemia; N=Study population; n=patients with hypoglycemic event; OR=odds ratio

[a] Longitudinal logistic linear regression adjusting for treatment period, sequence, and basal insulin dose, unless otherwise indicated

[b] Post-hoc analysis adjusting for mean daily BG resulted in an OR (95% CI) of 0.13 (0.04, 0.42; p<0.001)

[c] Prescott's test - significance could not be estimated using longitudinal logistic regression due to low event rate in BIL patients

Supported By: Eli Lilly and Company

937-P

Effects of Inhaled Technosphere Insulin (TI) on the Pulmonary Function of Patients with T1D and T2D

JOSEPH BRAIN, NIKHIL AMIN, JOHN STEWART, ELENA NIKONOVA, ROBERT WISE, *Boston, MA, Danbury, CT, Laval, QC, Canada, Morristown, NJ, Baltimore, MD*

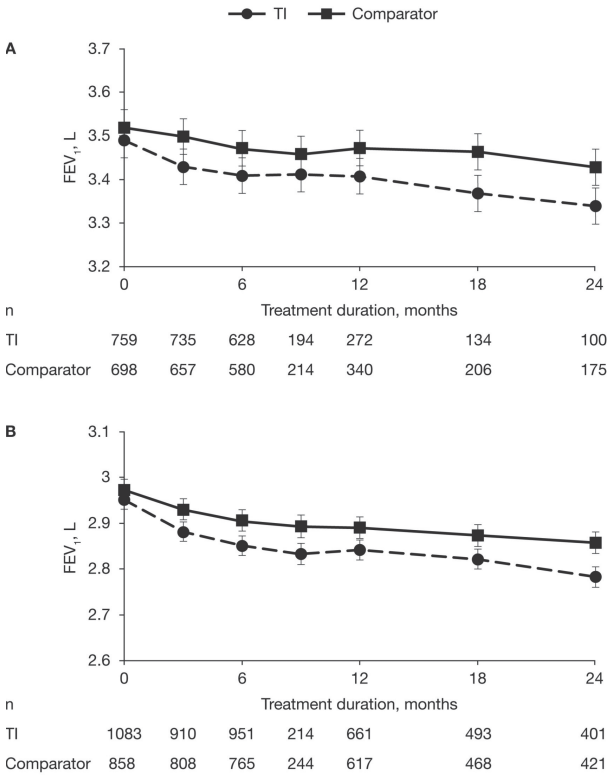
TI is a novel inhaled rapid-acting insulin (RAI) approved for use in the U.S. Management of spirometry may be a barrier to TI use, and there are concerns regarding declines in pulmonary function. This analysis explored spirometry data from clinical trials of TI.

Spirometry results were assessed using pooled analyses of 7 TI studies (duration 6-24 months). We included 1,842 patients with T1D (mean age 39 years; 51% male) and 2,281 with T2D (mean age 56 years; 56% male) using TI or comparator (RAI, standard of care, placebo).

Baseline mean (SD) forced expiratory volume in 1 second (FEV_1) values were 3.49 (0.787) L and 3.01 (0.714) L for patients with T1D and T2D, respectively. FEV_1 in both TI and comparator groups declined from baseline to 3 months in patients with T1D (TI = -0.063 L, comparator = -0.019 L; $P = 0.1414$) and T2D (TI = -0.084 L, comparator = -0.043 L; $P = 0.1431$) (Figure). After 3 months the decline in FEV_1 at each time point was comparable between TI and comparator groups. These reductions were a small percentage of the FEV_1, and not influenced by significant outliers. In 2 studies where FEV_1 was measured after discontinuation, there was no difference between groups after 1 month.

Our data, pooled from 7 clinical trials, demonstrate that TI's effects on pulmonary function are small and develop during the first 3 months of use. After that, TI and comparator groups demonstrate comparable physiologic declines for up to 24 months.

Figure. FEV_1 in Patients with T1D (A) and T2D (B) Treated with TI or Comparator.



Data represents LS means ± SE
Mixed effect model repeat measurement (MMRM) analyses were used; FEV_1, age, height and gender as covariates

Supported By: MannKind Corporation; Sanofi U.S.

ADA-Supported Research Moderated Poster Discussion

For author disclosure information, see page A696.

938-P

Impact of BMI on A1c Reduction in Response to IDegLira in Subjects with Type 2 Diabetes (T2D) Uncontrolled on SU, GLP-1RA, or Insulin Glargine: Analyses from Completed Phase 3b Trials

STEWART B. HARRIS, ELMAR JAECKEL, ESTEBAN JÓDAR, ILDIKO LINGVAY, KEVAL CHANDARANA, TRINE J. ABRAHAMSEN, CHRISTOPHER H. SORLI, *London, ON, Canada, Hannover, Germany, Madrid, Spain, Dallas, TX, Søborg, Denmark, Billings, MT*

Previous analyses of phase 3a trials (DUAL I extension; DUAL II) showed that insulin degludec/liraglutide (IDegLira) is efficacious irrespective of baseline body mass index (BMI) category in subjects with T2D who are insulin naïve or uncontrolled on basal insulin. This *post hoc* analysis aimed to confirm these findings in additional populations; T2D subjects uncontrolled on (i) glucagon-like peptide-1 receptor agonist (GLP-1 RA) (DUAL III: IDegLira vs. unchanged GLP-1 RA), (ii) sulfonylurea (SU) ± Metformin (DUAL IV: IDegLira vs. placebo) and (iii) insulin glargine (IG) (DUAL V: IDegLira vs. continued titration of IG from pre-trial dose). Starting dose of IDegLira was 10 dose steps [1 dose step = 1 U IDeg + 0.036 mg Lira] in DUAL IV and 16 dose steps in DUAL III and V; maximum IDegLira dose: 50 dose steps for all trials. This analysis of 3 trials grouped subjects by BMI category; <30, ≥30-<35 and ≥35 kg/m^2. In all 3 trials, change in A1c with IDegLira was similar between BMI groups (Table). Change in A1c was significantly greater with IDegLira vs. comparator in all BMI groups with a similar treatment difference between BMI groups (p=NS for all trials). This analysis confirmed IDegLira effectively reduced A1c across all baseline BMI categories when used in subjects previously treated with SUs (as an add on), GLP-1 RA or IG (all ± other oral therapies).

Table. Change in A1c by Baseline BMI Category in DUAL III, IV and V.

		Overall	BMI <30 kg/m^2	BMI ≥30–<35 kg/m^2	BMI ≥35 kg/m^2
DUAL III	**IDegLira, N**	292	84	110	98
	Baseline A1C,% (±SD)	7.8 (±0.6)	7.8 (±0.5)	7.8 (±0.6)	7.7 (±0.6)
	ΔA1C, % (±SD)	-1.3 (±0.8)	-1.4 (±0.9)	-1.4 (±0.9)	-1.3 (±0.8)
	GLP-1RA, N	146	36	59	51
	Baseline A1C,% (±SD)	7.7 (±0.6)	7.6 (±0.6)	7.8 (±0.7)	7.7 (±0.5)
	ΔA1C, % (±SD)	-0.3 (±0.9)	-0.5 (±0.8)	-0.4 (±1.0)	-0.2 (±0.9)
	ETD [95% CI]*	**-0.94 [-1.11;-0.78]**	**-0.78 [-1.12;-0.44]**	**-0.90 [-1.18;-0.61]**	**-1.06 [-1.32;-0.79]**
	***p* value**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
DUAL IV	**IDegLira, N**	289	119	102	68
	Baseline A1C,% (±SD)	7.9 (±0.6)	7.9 (±0.6)	7.9 (±0.6)	7.9 (±0.6)
	ΔA1C, % (±SD)	-1.5 (±0.8)	-1.4 (±0.8)	-1.4 (±0.8)	-1.6 (±0.9)
	Placebo, N	146	53	53	40
	Baseline A1C,% (±SD)	7.9 (±0.6)	8.0 (±0.6)	7.8 (±0.6)	7.9 (±0.6)
	ΔA1C, % (±SD)	-0.5 (±0.8)	-0.5 (±0.9)	-0.4 (±0.8)	-0.5 (±0.8)
	ETD [95% CI]*	**-1.02 [-1.18;-0.87]**	**-0.95 [-1.21;-0.68]**	**-1.07 [-1.32; -0.82]**	**-1.11 [-1.42; -0.81]**
	***p* value**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
DUAL V	**IDegLira, N**	278	99	110	69
	Baseline A1C,% (±SD)	8.4 (±0.9)	8.3 (±1.0)	8.3 (±0.8)	8.5 (±0.9)
	ΔA1C, % (±SD)	-1.8 (±1.1)	-1.8 (±1.1)	-1.8 (±1.2)	-1.9 (±0.9)
	IG, N	279	97	113	69
	Baseline A1C,% (±SD)	8.2 (±0.9)	8.3 (±1.0)	8.2 (±0.8)	8.3 (±0.8)
	ΔA1C, % (±SD)	-1.1 (±1.0)	-1.1 (±1.0)	-1.1 (±1.0)	-1.2 (±0.9)
	ETD [95% CI]†	**-0.59 [-0.74;-0.45]**	**-0.68 [-0.94; -0.42]**	**-0.52 [-0.76;-0.28]**	**-0.59 [-0.83;-0.34]**
	***p* value**	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**

Based on the full analysis set. Missing data is imputed using last observation carried forward. *Analyzed using ANCOVA with treatment, previous antidiabetic therapy and region as fixed factors and baseline A1C as covariate. †Analyzed using ANCOVA with treatment and region as fixed effects and baseline A1C as covariate. A1C, glycated hemoglobin; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; N, number of subjects; SD, standard deviation

Supported By: Novo Nordisk Inc.

939-P

Association between Postprandial Glucose and A1c following Biphasic Insulin Aspart 30 Treatment

PAUL VALENSI, BRIAN LARSEN THORSTED, LISE LOTTE NYSTRUP HUSEMOEN, JAMES WEATHERALL, LOUIS MONNIER, *Bondy, France, Søborg, Denmark, Plainsboro, NJ, Montpellier, France*

The study aimed to investigate an association between self-measured postprandial glucose (PPG) 2 h after breakfast and A1c in people with type 2 diabetes, who started on biphasic insulin aspart 30 (BIAsp 30) in the 26-week, international, observational IMPROVE study (n=49,236). Pre-study therapies included no pharmacological therapy (16.1%), oral antidiabetics (OADs) only (63.0%) or insulin ± OAD (20.9%). Mean (±SD) age and diabetes duration were 55.6±12.0 and 7.4±6.4 years, respectively; 44% of patients were men and mean (±SD) body mass index was 26.4±4.9 kg/m^2. At final visit, A1c decreased by 2.2% from 9.3±1.8%, fasting plasma glucose by 4.1 mmol/L from 10.8±3.2 mmol/L and PPG (breakfast) by 6.3 mmol/L from 14.8±4.5 mmol/L. At final visit, adjusted multivariate analysis showed a significant association between PPG (breakfast) and A1c (beta coefficient 0.11, $p<.0001$) in the overall population; thus, for a change of 1 mmol/L in PPG, HbA_{1c} would be expected to change by 0.11%. The association was persistent across countries and also found at baseline (Table).

In conclusion, in people with type 2 diabetes and poor glycemic control, there was a significant association between PPG (breakfast) and HbA_{1c}. The association remained after 26 weeks of BIAsp 30 despite A1c improvement.

Table. Estimates of the Association between PPG (Breakfast) and A1c.

Country	Final visit*		Baseline visit – all**	
	Estimate (*p*-value)	R^2	Estimate (*p*-value)	R^2
Overall	0.11 (<.0001)	0.35	0.09 (<.0001)	0.22
Canada (n=1334)	0.07 (<.0001)	0.35	0.09 (<.0001)	0.22
China (n=19228)	0.17 (<.0001)		0.09 (<.0001)	
Greece (n=951)	0.12 (<.0001)		0.07 (0.1598)	
India (n=16322)	0.07 (<.0001)		0.08 (<.0001)	
Italy (n=1265)	0.13 (<.0001)		0.14 (<.0001)	
Japan (n=1679)	0.10 (<.0001)		0.13 (<.0001)	
Poland (n=3821)	0.12 (<.0001)		0.12 (<.0001)	
Russia (n=4684)	0.23 (<.0001)		0.14 (<.0001)	

BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; OAD, oral antidiabetic drug.

*Adjusted for age, BMI, diabetes duration, sex, country and FPG at final visit.

**Adjusted for age, BMI, diabetes duration, sex, country, pre-study therapy and FPG at baseline.

Supported By: Novo Nordisk A/S

940-P

Glargine Insulin Use vs. Continuous Regular Insulin in Diabetic Surgical Non-Critically Ill Patients Receiving Parenteral Nutrition (GLUCOSE-in-PN): Randomized, Controlled Study

HAKEAM A. HAKEAM, *Riyadh, Saudi Arabia*

Background: Hyperglycemia is a major complication of parenteral nutrition (PN). Guidelines for hyperglycemia management in non-critically ill hospitalized patients recommend basal insulin administration but no regimen specified. The aim of this study was to compare the efficacy of glargine insulin vs. continuously infused regular insulin in PN (RI-in-PN) to achieve glycemic control in diabetic, non-critically ill, surgical patients receiving PN.

Methods: This is a prospective, randomized, open-label study. Non-critically ill, surgical, diabetic patients receiving PN were randomized to receive basal glargine insulin or RI-in-PN on day 4 of PN support. Mean blood glucose levels were compared on study days 5 to 9. The percentage of blood glucose measurement at goal was compared between groups.

Results: A total of 67 PN treatment episodes were analyzed. There were no statistically significant differences in mean glucose levels between groups on any study day ($P>0.1$). Overall glycemic control rate were 52.24% and 47.76% for the glargine insulin and RI-in-PN groups, respectively ($P=0.06$). The percentage of blood glucose measurements > 234 mg/dL was higher for the glargine insulin group compared to the RI-in-PN group (3.28% vs. 0.6%; $P=0.017$). Based on blood glucose, there were six hypoglycemic events: two in the glargine insulin group (5.7%) and four in the RI-in-PN group (11.4%) ($P>0.1$).

Conclusion: Both glargine insulin and RI-in-PN are effective basal insulin modalities for blood glucose control in diabetic, non-critically ill, surgical patients receiving PN. Hyperglycemic spikes occurred more frequently with glargine insulin, and the rate of hypoglycemia was acceptable for both regimens.

941-P

Predictors of Drug-Free Diabetes Remission over 48 Weeks following Short-Term Intensive Insulin Therapy (IIT)

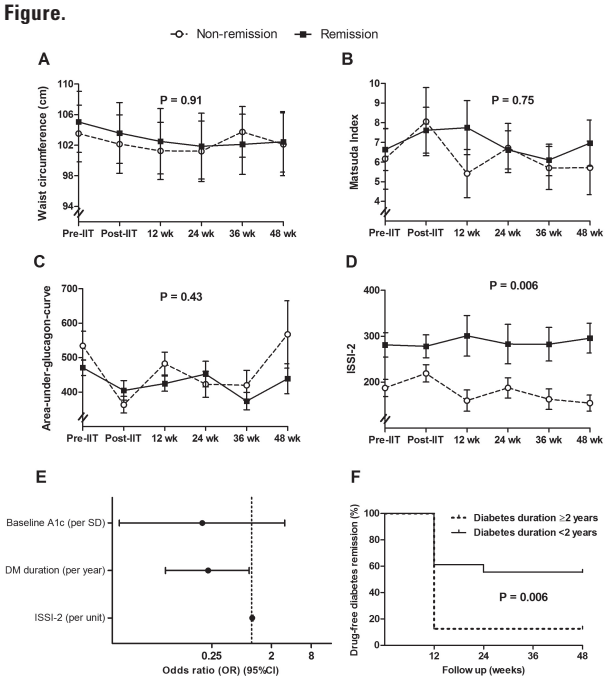
CAROLINE K. KRAMER, BERNARD ZINMAN, HAYSOOK CHOI, RAVI RETNAKARAN, *Toronto, ON, Canada*

In early T2DM, short-term IIT can induce a remission of diabetes that can last up to 1 year in some patients. However, little is known about the predictors of such a sustained response. To address this question, we evaluated data from the placebo arm of a double-blind RCT in which patients with early T2DM underwent 4 weeks of IIT (basal detemir and bolus aspart), followed by placebo therapy (n=25) for 48 weeks. Patients were assessed by oral glucose tolerance test (OGTT) every 12 weeks. Diabetes remission was defined as A1c <6.5% on no medication for T2DM. At 48 weeks, there were 14 patients in remission. Comparison of remitters to non-remitters revealed no differences over 48 weeks in waist, insulin sensitivity (Matsuda index), or area-under-the-glucagon-curve on OGTT (Figure A-C). However, compared to their peers, the remission group showed preservation of beta-cell function (Insulin Secretion-Sensitivity Index-2 (ISSI-2)) across the 48 weeks (P=0.006) (Figure D). On logistic regression analyses, diabetes duration supplanted beta-cell function as an independent predictor of remission (Figure E). In particular, diabetes duration <2 years predicted persistence of remission (P=0.006) (Figure F). These observations suggest that, early in the course of T2DM, there is sufficient reversibility in the disease process to enable the achievement of sustained drug-free diabetes remission following short-term IIT.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

Figure.



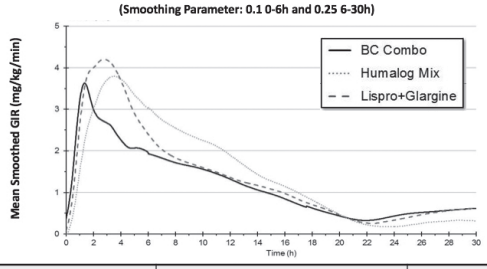
942-P

Pharmacodynamic (PD) Profile of BioChaperone® Combo (BC Combo), a New Combination Rapid-Acting and Long-Acting Insulin, in Subjects with Type 2 Diabetes Mellitus (T2DM)

ULRIKE HOEVELMANN, ANNELIE FISCHER, OLIVER KLEIN, GREGORY MEIFFREN, BERTRAND ALLUIS, CLAIRE MEGRET, MARTIN GAUDIER, OLIVIER SOULA, SIMON BRUCE, EDA CENGIZ, TIM HEISE, *Neuss, Germany, Lyon, France, San Diego, CA, New Haven, CT*

BC Combo is a co-formulation of 25% lispro (LIS) and 75% glargine (GLA). We characterized the glucose-infusion rate (GIR) profiles of 0.8 U/kg BC Combo, 0.8 U/kg 75% lispro protamine suspension (Humalog® Mix 75/25™ (HMx)) or separate simultaneous injections of 0.2 U/kg LIS and 0.6 U/kg GLA in 24 subjects with T2DM (fasting C-peptide<1.0 nmol/l) in a double-blind, randomized, double-dummy, cross-over study using the automated euglycemic glucose clamp technique [ClampArt®, target blood glucose 100 mg/dL, clamp duration 30 hours). Early ($AUC_{GIR0\text{-}2h}$) and late ($AUC_{GIR24\text{-}30h}$) pharmacodynamic effects were similar for BC combo and LIS+GLA but greater vs. HMx. Time to peak action (T_{GIRmax}) was faster with BC Combo and LIS+GLA vs. HMx. In conclusion, BC Combo demonstrated a significantly higher early (prandial) and late (basal) metabolic activity vs. HMx, comparable to separate injections of LIS and GLA in subjects with T2DM. Based on these results BC Combo can improve both fasting and postprandial glucose control vs. HMx and/or provide a once-daily injection that provides basal + one meal coverage.

Figure. Glucose-Infusion Rate Profiles over 30-hours after Dosing Study Treatment.



Parameter N =24	BC Combo	Humalog Mix 25/75 (HMx)	P-value vs. BC Combo	Lispro + Glargine (LIS + GLA)	P-value vs. BC Combo
Early $AUC_{GIR0\text{-}2h}$ (mg/kg/min)	235	149	**0.0001**	202	NS
Late $AUC_{GIR24\text{-}30h}$ (mg/kg/min)	176	48	**0.01**	154	NS
T_{GIRmax} (h)	1.3	3.8	**<0.0001**	2.9	0.006
Total $AUC_{GIR0\text{-}30h}$ (mg/kg/min)#	1801	2220	**0.01***	2208	0.01*

Hodges & Lehmann Estimates, #Least Mean Square, * LSM Ratio

943-P

Real-World Assessment of Patient Characteristics and Clinical Outcomes of Early Users of the New Insulin Glargine 300 U/mL

FEN YE, RISHI AGARWAL, AMNEET KAUR, RISHAB GUPTA, MEHUL R. DALAL, JENNIFER SUNG, PAULOS BERHANU, *King of Prussia, PA, Florham Park, NJ, Cambridge, MA, Bridgewater, NJ*

The new basal insulin glargine 300 U/mL (Gla-300) is a formulation of insulin glargine that has a more constant pharmacokinetic profile with a prolonged duration of action, compared with insulin glargine 100 U/mL. Gla-300 for the treatment of diabetes entered the U.S. market in 2015 based on data from the EDITION clinical trial program. In this study, we further assessed the effectiveness of Gla-300 in the management of type 2 diabetes (T2D) in the real-world setting.

Patient-level data from people with T2D who used other basal insulins within the 6 months prior to Gla-300 initiation (defined as having ≥ 1 prescription order of Gla-300 between March 2015 and December 2015) were extracted from the Predictive Health Intelligence Environment database, which includes 24 U.S.-based integrated delivery networks. Hypoglycemic events were identified based on ICD-9-CM diagnosis codes or blood glucose ≤ 70 mg/dL. Data were assessed for up to 6 months prior to and up to 6 months after Gla-300 initiation.

Of the 881 patients identified, 53.3% were male, 59.4% were Caucasian, and mean age was 59.6 years. Comorbid hypertension (86%), dyslipidemia (88%), and diabetes-related complications (neuropathy [35%], nephropathy [17%], and retinopathy [11%]) were prevalent. Among the subset of patients (n = 267) with A1c measured at baseline and during follow-up, mean A1c decreased from 8.97% at baseline (0-6 months) to 8.33% at follow-up (0-6 months), with a mean estimated reduction of 0.64%, 95% CI (0.45, 0.84) (P < 0.0001). Switching to Gla-300 was also associated with a decreased occurrence of hypoglycemia (6.0% vs. 5.1%, baseline vs. follow-up [both 0-3 months; n = 449)].

In real-world settings, switching to Gla-300 from other basal insulins was associated with improved glycemic control and a trend towards less hypoglycemia in patients with T2D.

Supported By: Sanofi U.S.

944-P

Sortase A-mediated Synthesis of Insulin Fusion Derivatives from a New Insulin Precursor

DANNY HUNG-CHIEH CHOU, MARIA DISOTUAR, *Salt Lake City, UT*

Currently, fast-acting insulin and long-acting insulin are available clinically for people with diabetes to provide better glycemic control. Among them, the success in the development of insulin detemir and degludec highlights the use of chemically modified insulin derivatives as the next-generation therapeutics. For example, we recently reported phenylboronic acid-containing insulin derivatives that exhibit better glycemic control compared to insulin detemir in T1D mouse models[1]. However, although several methods to synthesize insulin derivatives have been reported, these methods suffer from low yields and have limited functional tolerance. Therefore, we aim to develop a new method for the synthesis of insulin derivatives with high efficiency and functional group tolerance. Sortase A is a thiol-containing transpeptidase that recognizes an LPXTG sequence and cleaves the threonine-glycine bond to form a thioacyl-linked intermediate, which is primed to react with the N-terminal oligoglycine motif in high efficiency. The insulin B-chain sequence ends with TPKT (B27-30). Des B27-30 insulin was reported to have full activity, which suggests that this segment of insulin is not involved in its bioactivity. Therefore, we synthesized a new insulin analog ending with LPKTGGG (Ins-SA), which has a similar potency as native insulin in activating the insulin signaling pathway using pAkt as a readout. Using Ins-SA, we have synthesized a series of insulin fusion derivatives that maintain the bioactivity in high yields (70-80%). Among them, Ins-SA-ALB is an albumin binding insulin that demonstrates long-lasting properties in STZ-treated C57BL/6 mice. We also synthesized an insulin-GLP-1 fusion protein that activates both insulin receptor and GLP-1 receptor. In summary, this sortase-mediated method provides a new approach to synthesize insulin derivatives in high efficiency.

Supported By: American Diabetes Association (1-16-JDF-018 to D.H-C.C.); JDRF

945-P

Differential Insulin Concentrations in the Injected NPH from Vials and Cartridges: Dependency on Prior Resuspension

PAOLA LUCIDI, FRANCESCA PORCELLATI, ANNA MARINELLI ANDREOLI, PAOLA CANDELORO, PATRIZIA CIOLI, GEREMIA B. BOLLI, CARMINE G. FANELLI, *Perugia, Italy*

This study aimed at evaluating the insulin concentration ($Ins_{[C]}$) of the injected NPH either re-suspended (R+) or not re-suspended (R-) in different vials/cartridges from major insulin companies.

Results: The NPH_R+ was homogeneous, whereas NPH_R- separated into a clear (top) and cloudy (bottom) part (vials/cartridges hold vertically). In vials, as compared to the $Ins_{[C]}$ of NPH_R+ (assumed as 100%), the clear NPH_R- had $Ins_{[C]}$ <3%, but the cloudy part had 202±24% and 291±32% (Novo and Lilly, respectively). In pen cartridges, percentages were similar (clear part <3%; cloudy part 228±19, 166±15, 462±38%; Novo, Lilly, Sanofi). $Ins_{[C]}$ in NPH_R+ and NPH_R- (clear and cloudy parts) highly correlated with PK/PD in T1DM (p<0.001). With vials hold vertically, the time required to observe 50% of separation of cloudy from clear part at 4 °C, was longer with Novo (55±7 min) vs. Lilly NPH vial (18±3 min) (p=0.021); it was independent from the different diameter of the vials, and at room temperature, the process became faster in Lilly vial (11.5±2.1 min), but slower in Novo vial (210±35 min p=0.015). With pen cartridges, this process was faster vs. vials. The time needed to re-suspend NPH (seconds spent in tipping) was similarly short with Novo (5±1 s) and Lilly vials (6±1 s), but longer with pen cartridges (50±8, 40±6 and 30±4 s, Novo, Lilly and Sanofi) (p=0.022).

Conclusions: The different PK/PD of NPH_R+ vs. NPH_R- *in vivo* in T1DM, are dependent on the differential $Ins_{[C]}$ of injected NPH. Knowledge of modalities for appropriate re-suspension of NPH in vials and cartridges from different companies, is important to avoid PK/PD variability of injected NPH.

946-P

A Single-Dose Euglycemic Clamp Study in Subjects with Type 1 Diabetes Demonstrating Pharmacokinetic and Pharmacodynamic Similarity between MK-1293 Insulin Glargine and Originator Insulin Glargine (Lantus)

MICHAEL CRUTCHLOW, JOHN PALCZA, KATE MOSTOLLER, CHANTAL MAHON, APRIL M. BARBOUR, MICHAEL MARCOS, YANG XU, LINDA MORROW, MARCUS HOMPESCH, *Kenilworth, NJ, Chula Vista, CA*

MK-1293 is a biosimilar insulin glargine under development using Lantus as the originator benchmark. This double-blind, randomized, two-treatment, four-period replicate crossover euglycemic clamp study in 76 male and female subjects (age: 18-65 years, BMI: >18.0 and ≤30.0 kg/m^2) with type 1 diabetes mellitus (T1D) was conducted to demonstrate pharmacokinetic (PK) and pharmacodynamic (PD) similarity between MK-1293 and Lantus procured in the European Union. In each period, patients received single 0.4 units/kg doses of MK-1293 or Lantus followed by a 30-hour assessment period for PK and euglycemic clamping (clamp target 130 mg/dL). An LC-MS/MS assay was used to quantify concentrations of the M1 glargine metabolite. Predefined similarity criteria included the 90% confidence interval (CI) for the geometric mean ratio of M1 falling between 0.8 and 1.25 for the primary PK parameters and the 95% CI for the arithmetic mean ratio falling between 0.8 and 1.25 for the glucose infusion rate (GIR)-based primary PD parameters. Similarity criteria were met for each of these primary endpoint comparisons (Table). Both treatments were well tolerated and there were no serious adverse events. This study successfully demonstrated PK and PD similarity between MK-1293 and Lantus in T1D.

Table.

		MK-1293/Lantus
PK Endpoints[1]		
Primary	$AUC_{0\text{-}24hr}$	0.97 (0.91, 1.02)
	C_{max}	0.97 (0.93, 1.03)
Secondary	$AUC_{0\text{-}12hr}$	0.92 (0.86, 0.97)
	$AUC_{12\text{-}24hr}$	1.00 (0.95, 1.04)
PD Endpoints		
Primary	GIR $AUC_{0\text{-}24hr}$	0.95 (0.88, 1.01)
	GIR $AUC_{0\text{-}12hr}$	0.90 (0.81, 0.99)
	GIR $AUC_{12\text{-}24hr}$	0.99 (0.92, 1.06)
	GIR_{max}	0.96 (0.91, 1.02)

[1]Primary and secondary PK endpoints are derived from plasma concentrations of the M1 glargine metabolite which is the primary circulating active glargine species. PK endpoint results presented as geometric mean ratios and 90% confidence intervals. GIR-based PD endpoint results presented as arithmetic mean ratios and 95% confidence intervals. GIR=glucose infusion rate; GIR_{max}= maximal glucose infusion rate.

Supported By: Merck & Co., Inc.

947-P

Underlying Mechanisms for Long-Acting Properties of the Novel Weekly Insulin HM12470

SANG YOUN HWANG, JUNG KUK KIM, JIN YOUNG KIM, IN YOUNG CHOI, MARCUS HOMPESCH, SE CHANG KWON, *Hwaseong, Republic of Korea, Chula Vista, CA*

The ultra long-acting basal insulin, HM12470, has been developed by conjugating an insulin analog (Insulin 115) with the constant region of a human immunoglobulin fragment (Fc) via non-peptidyl linker. Previously, we demonstrated that HM12470 had longer PK/PD properties than HM12460A (human insulin conjugated with Fc) in various animal models. However, the mechanism of prolonged properties remained to be fully elucidated. This study investigated the underlying molecular mechanisms of the long-acting properties of insulin 115 and HM12470 in comparison with human insulin and HM12460A. Firstly, we demonstrated that insulin 115 and HM12470 had lower affinity to the human insulin receptor-B than human insulin and HM12460A. Similar results were observed when comparing receptor phosphorylation and internalization [insulin 115 (85.5%, 78.5%, 84.3%), HM12470 (1.70%, 2.64%, 27.8%), HM12460A (2.64%, 6.41%, 40.4%); relative activity vs. human insulin for receptor binding, phosphorylation, and internalization, respectively]. The reduced *in vitro* activities were well correlated with cellular stability in HepG2 cells. The residual amount of insulin 115 (86%) and HM12470 (97%) was higher than that of human insulin (20%) and HM12460A (78%) in conditioned media. These results implied that insulin 115 and HM12470 with relatively lower receptor affinity could induce less receptor mediated clearance (RMC) when considering that the receptor binding affinity is correlated with RMC. Lastly, the serum stability of Insulin 115 and HM12470 was evaluated, and both insulin 115 (59%) and HM12470 (70%) showed higher % residual levels than human insulin (8%) and HM12460A (49%) after prolonged incubation in human serum. Therefore, our results suggest that the long-acting properties of insulin 115 and HM12470 are based on combined effects of both reduced *in vitro* activity, less internalization, and improved stability in the cellular/serum compartments.

948-P

Comparison of the Effect of Humulin R and Lispro on Glucose Regulatory Hormones and Thermogenesis

IVONA DASKALOVA, DAVID ROBBINS, ROBERT E. RATNER, TZVETELINA TOTOMIROVA, NIKOLAY PETROV, *Sofia, Bulgaria, Kansas City, KS, Alexandria, VA*

Diabetes is a result of insulin deficiency or resistance along with absolute or relative excess of glucagon. Exogenous administration of insulin could have additional effects on glucose regulatory hormones and could improve glucose disposal and meal induced thermogenesis. We studied 12 patients with type 2 diabetes, mean age 46.1±7.2 years, 6.2±8.8 years disease duration, mean BMI 34.2±4.6 kg/sq. m. Their own oral medication was stopped 2 weeks prior to the study. In four different days patients received randomly subcutaneous application of insulin as follows: on -30 minute diluent/0 minute insulin lispro; -30 minute diluent/0 minute diluent; -30 minute diluent/0 minute humulin R; -30 minute humulin R/0 minute diluents in dose 0.1U/kg prior to standardized meal. Blood glucose (mg%), insulin (mcU/ml), C-peptid (ng/ml) and glucagon (pg/ml) are measured on -10, 0, 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300 minute. Continuous energy expenditure was measured with Delta Track Metabolic Cart method. Insulin lispro reaches higher peak insulin level (71.25±16.75mcU/ml) approximately on 60 minute compared to Humulin R groups (54.28±19.14mcU/ml, p<0.005; 58.63±20.86mcU/ml, p<0.005) achieved usually between 45 and 90 minute. Lispro showed better effect on lowering of glucagon secretion (AUC 32864.18±8764.18 vs. 35132.7±7669.13 and 35411.18±6563.33, p<0.05). Difference in C-peptide level was found only between groups on lispro and hmulin R applied 30 minutes before meal (AUC 1070.4±371.7 vs. 985.1±360.95, p=0.003). Meal induced thermogenesis was greater (p<0.001) following insulin lispro compared to humulin R groups. In conclusion insulin lispro applied at mealtime shows better potential for controlling patophysiologic disregulations in type 2 diabetes compared to humulin applied 30 minutes previously or at mealtime.

949-P

Dapagliflozin Induces Ketosis in Patients with Type 1 Diabetes

HUSAM GHANIM, NITESH D. KUHADIYA, SALMAN KHAN, MANISHA GARG, KELLY GREEN, SANAA ABUAYSHEH, PARESH DANDONA, *Buffalo, NY*

We have now investigated triple therapy in type 1 diabetes (T1D) using a sequential combination of insulin, liraglutide and dapagliflozin. Since treatment with SGLT2 inhibitors in T1D is associated with increased risk of diabetic ketoacidosis (DKA), we investigated the effect of dapagliflozin on mediators of ketosis in patients on triple therapy. 30 T1D patients on insulin and liraglutide therapy for at least last 6 months were randomized (in 2:1 ratio, drug: placebo) to receive either dapagliflozin 10mg or placebo daily for 12 weeks

For author disclosure information, see page A696.

(dapagliflozin initiated at 5mg daily for first week). 26 patients completed the study (Placebo=9; Dapagliflozin=17). While there was a decrease in HbA1c of 0.6±0.1% ($p<0.01$ vs. placebo); there was a significant increase in glucagon concentrations by 35±13% (from 91±12 to 114±19pg/ml, $p<0.05$), hormone sensitive lipase (HSL) by 29±11% (from 4.9±0.7 to 16.3±0.78ng/ml, $p<0.05$), FFA (from 0.34±0.04 to 0.59±0.11mM; $p<0.05$), acetoacetate (from 0.32±0.09 to 0.53±0.11mM, $p<0.05$) and β-hydroxybutyrate (β-OHB) (from 0.11±0.02 to 0.39±0.09mM, $p<0.05$) while there was no change in the placebo group. Total urinary ketones (acetoacetate and β-OHB) levels also increased significantly from 0.68±0.19 to 1.28±0.34μM/mg creatinine ($p<0.05$) with unchanged plasma bicarbonate concentrations and mean total insulin dose in either group. Serum β-OHB levels were related to FFA concentrations ($r=0.374$, $p<0.05$) and inversely to total insulin dose at 12 weeks ($r=-0.297$, $p<0.05$) but not to HSL or glucagon levels. Two of the drop-out patients in the dapagliflozin group suffered from DKA within a day after increasing the dose of dapagliflozin to 10mg (one with euglycemic DKA and other with hyperglycemic DKA). We conclude that all patients treated with dapagliflozin experienced increased lipolysis stimulated by glucagon and HSL and increased ketogenesis not amounting to DKA. Caution needs to be exercised while decreasing insulin doses and increasing dapagliflozin doses as it resulted in DKA in two patients.

950-P

Glucose Control and Safety of Different Basal Insulin Therapies in Real-World Setting: ORBIT Study in China

LINONG JI, PUHONG ZHANG, DONGSHAN ZHU, XIAOHUI GUO, JUMING LU, WENYING YANG, JIANPING WENG, SATISH K. GARG, *Beijing, China, Guangzhou, China, Aurora, CO*

Insulin NPH, glargine and detemir are the most commonly used basal insulin (BI). We report the largest 6-month registry study in China to compare their real life safety and effect of glucose control. 18,995 patients with T2DM inadequately controlled (HbA1c and age; 7%) on OADs were enrolled from 209 hospitals and followed at 3 and 6 months during 2011-2013. Patients who initiated BI and kept using the same BI without adding any other type of insulin during 6 months were used for analysis. Type and dose of BI were at the physician's discretion and patients' willingness. Propensity scores (PS) regression adjustment method was used to adjust the baseline differences among the three groups.

9002 patients met the requirement with mean age 55.6 ± 10.1 years, men 54.0%, mean A1c 9.2 ± 1.8%, mean FPG 199.8 ± 63 mg/dl and mean duration of diabetes 6.5 ± 5.1 years. There were 6804, 1122 and 1076 patients continued using Glargine, Detemir and NPH insulin respectively. Baseline variables were well balanced in the three groups after PS adjustment. After PS regression adjustment and covariates control, the glucose control and safety of three types of BI are shown in Table 1.

In real world setting, initiating glargine or determir associates with better HbA1c reduction than NPH insulin. Glargine insulin has the lowest minor hypoglycemia whereas determir insulin was associated with the least weight gain.

Table 1. Glucose Control and Safety of Three Types of Basal Insulin after Initiation for 6 Months.[a]

	Total	Insulin Glargine	Insulin Determir	NPH insulin	P value			
	(N=9002)	(N=6804)	(N=1122)	(N=1076)	Over all	Glargine vs.Determir	Glargine vs.NPH	Determir vs. NPH
HbA1c level(%), mean±SD								
Mean level at 6 month	7.3 ± 1.3	7.3 ± 1.3	7.3 ± 1.3	7.5 ± 1.4	<.0001	0.7388	<.0001	<.0001
Change from baseline	-1.9 ± 1.8	-2.0 ± 1.9	-2.0 ± 1.9	-1.7 ± 2.0	0.0002	0.8441	<.0001	0.0022
HbA1c target (<7.0%) achieved (%)	44.1	44.3	46.1	40.5	0.0445	0.2663	0.0378	0.0146
FPG level (mg/dl), mean±SD								
Mean level at 6 month	136.3 ± 40.3	135.4 ± 40.4	136.8 ± 41.6	140.3 ± 42.4	0.007	0.0435	0.0017	0.0933
Change from baseline	-63.5 ± 66.6	-66.1 ± 66.6	-68.4 ± 68.6	-58.8 ± 69.8	0.0083	0.4221	0.0043	0.0066
FPG target (<7.0 mmol/L) achieved (%)	47.5	48.7	46.3	41.6	0.0014	0.2666	0.0004	0.0795
Weight (kg)								
Mean level at 6 month	67.7 ± 10.4	67.7 ± 10.5	67.5 ± 10.6	67.7 ± 11.2	0.8067	0.5123	0.9456	0.6712
Change from baseline	0.0 ± 2.7	0.1 ± 2.7	-0.2 ± 2.7	0.0 ± 2.9	0.0124	0.0031	0.8461	0.045
Severe hypoglycemia (%) [b]	0.2	0.2	0.2	0.1	0.3374	0.6195	0.1554	0.306
Minor hypoglycemia (%) [b]	7.7	6.1	9.3	11.8	<.0001	<.0001	<.0001	0.0768

a: Propensity score regression adjustment method were used to adjust baseline characteristics. Propensity score calculation was based on variables of hospital level, gender, age, body weight, diabetes duration, residence, medical insurance, and HbA1c, FPG, diabetes complication, OAD number at baseline. Covariates of basal insulin dose at visit 3 was also controlled. b: The proportion of patients who reported severe hypoglycemia in previous 3 months and minor hypoglycemia in previous 1 month at visit 3, respectively.

Supported By: Sanofi-Aventis China

951-P

WITHDRAWN

952-P

Good Perioperative Glycemic Control with Low Hypoglycemia Rates Can Be Achieved in Cardiac Surgery Patients with a Computerized Intravenous Insulin Algorithm

ALVIN WAI KIT TAN, JENNIFER L. KIRBY, JAMES M. ISBELL, ANTHONY L. MCCALL, *Charlottesville, VA*

In cardiac surgery patients, insulin use for glycemic control has been shown to improve surgical outcomes. A 2-year retrospective analysis was conducted on data from a single institution, which implemented a computerized intravenous (IV) insulin algorithm (Glucommander). The aim was to evaluate Glucommander's effectiveness with a particular focus on hypoglycemia, using Glucommander-generated reports and manually collected data. Glucommander was used in 1652 cardiac surgery patients with 82,335 blood glucose (BG) readings over 1667 hospital admissions. The average time to target BG (120-160 mg/dl) was 87 min. The mean BG achieved was 138 ± 33 mg/dl, with 61.5, 4.4 and 0.47% of BG 100-140, >200 and ≤70 mg/dl respectively. The incidence of hypoglycemia (BG ≤70 mg/dl) was 0.19 episode/admission with 322 hypoglycemia episodes occurring in 224 patients, of which only 3.4% were severe (≤40 mg/dl). Of the 224 patients (median age 66, median eGFR 68ml/min/1.73m^2 and median alanine transaminase level 21U/L), 44.2% had known or newly-diagnosed diabetes mellitus (DM) with median HbA1c 7.2%, while 26.3% had pre-DM. Hypoglycemia incidence and proportion of patients with hypoglycemia were lower in the second year compared to the first (0.12 vs. 0.27 episode/admission; 8.8 vs. 18.1%; both $p<0.001$). All 11 severe hypoglycemia episodes occurred in the first year. Mean BG, percentage of BG >200 mg/dl and time to target BG were similar in both years. The reduced hypoglycemia frequency was partly due to algorithm adjustments in the second year, including the use of a lower multiplier to calculate initial insulin rate. In conclusion, a computerized IV insulin algorithm can achieve good perioperative glycemic control with low hypoglycemia rates in cardiac surgery patients. Regular post-implementation audits are important for modifications to further reduce hypoglycemia frequency and severity without affecting overall glycemic control.

953-P

Comparison of Lixisenatide-Treated Caucasian and Latino/Hispanic Patients with T2D in the GetGoal Trials

GUILLERMO E. UMPIERREZ, TERRY DEX, ELENA NIKONOVA, MARIAM ABOUHOSSEIN, JASON CHAO, JAIME DAVIDSON, *Atlanta, GA, Bridgewater, NJ, Morristown, NJ, Dallas, TX*

Lixisenatide is a once-daily injectable glucagon-like peptide-1 receptor agonist in development for the treatment of diabetes in the U.S. There is variation among ethnic groups regarding diabetes prevalence, complications, drug responses, and outcomes. The aim of this post-hoc analysis was to compare the outcomes for lixisenatide-treated Caucasian and Hispanic patients (pts) with T2D.

In this pooled analysis of 3 multinational GetGoal trials (GetGoal Duo-1, GetGoal Duo-2 and GetGoal-L), data from pts with T2D on lixisenatide as add-on therapy to basal insulin were sorted and grouped by ethnicity (Caucasian [n = 496] or Hispanic [n=209)].

There were no differences in A1c at baseline and at the end of the studies for lixisenatide-treated Caucasian vs. Hispanic pts (Table). Caucasian pts had higher average body weight at baseline and after lixisenatide treatment compared with Hispanic pts and greater change in body weight (Table). By the end of the studies there were no significant differences between percent of pts experiencing ≥ 1 symptomatic hypoglycemia event (< 60 mg/dL), insulin dose change, percent achieving 2-hour postprandial glucose < 180 mg/dL, and those achieving composite endpoint of A1c < 7.0% with no weight gain and no symptomatic hypoglycemia (Table).

These results indicate that there are comparable safety and efficacy outcomes for Caucasian and Hispanic pts treated with lixisenatide.

Table. Baseline, Change, and Endpoint Values for Caucasian and Hispanic Lixisenatide-Treated Pts With T2D.

	Caucasian		Hispanic		
Characteristics	**N**	**Statistics**	**N**	**Statistics**	***P* Value[a]**
Age, years (SD)	495	59 (8.90)	209	58 (9.39)	0.3807
Male, n (%)	495	247 (49.9)	209	72 (34.4)	0.0002
Duration of diabetes, years (SD)	495	11.2 (6.74)	209	12.8 (6.33)	0.0040
Baseline A1c, % (SD)	482	7.9 (0.77)	197	8.0 (0.74)	0.9330
End of study A1c, % (SD)	482	7.3 (0.99)	197	7.3 (0.86)	0.3714
A1c change from baseline, % (SD)	482	–0.6 (0.87)	197	–0.7 (0.80)	0.3812
Baseline weight, kg (SD)	485	94.7 (18.96)	202	80.9 (17.13)	< 0.0001
Weight change from baseline, kg (SD)	485	–1.1 (4.51)	202	–0.3 (2.82)	0.0096
Insulin dose at baseline, U (SD)	490	61.0 (34.56)	208	51.5 (22.75)	0.0017
Insulin dose change, U (SD)	490	–0.3 (19.08)	208	–1.2 (9.09)	0.6478
Pts with symptomatic hypoglycemia (< 60mg/dL), n (%)	496	152 (30.6)	209	79 (37.8)	0.1222
Pts achieving postprandial glucose[b] goal < 180mg/dL, n (%)	279	137 (49.1)	136	71 (52.2)	0.4507
Pts with A1c < 7.0%, no weight gain, no symptomatic hypoglycemia, n (%)	495	63 (12.7)	209	15 (7.2)	0.2073

Data are mean (SD). [a]*P* values for categorical endpoints were from Cochran-Mantel-Haenszel test, stratified by study, and those for continuous endpoints were from 2-way analysis of variance with study and ethnicity as factors. [b]Measured 2 hours after a standard liquid meal in a subset of pts.

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954-P

Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed-Ratio Combination in Elderly Patients with T2D

YEHUDA HANDELSMAN, CHRISTINA CHOVANES, TERRY DEX, FRANCESCO GIORGINO, NEIL SKOLNIK, ELISABETH SOUHAMI, WILLIAM STAGER, JUAN PABLO FRIAS, *Tarzana, CA, Abington, PA, Bridgewater, NJ, Bari, Italy, Paris, France, Los Angeles, CA*

T2D is common in the elderly and related to increased mortality and morbidity if suboptimally controlled. This post-hoc study assessed the efficacy and safety in elderly patients (pts) of once-daily LixiLan, a titratable fixed-ratio combination of insulin glargine 100 U/mL (Gla-100) and lixisenatide in development to manage fasting and postprandial plasma glucose (FPG and PPG). Data from pts aged ≥ 65 years, with T2D, were derived from two 30-week phase 3 clinical trials with LixiLan in pts uncontrolled on Metformin ± oral antidiabetes drugs (OADs) (LixiLan-O) or basal insulin ± OADs (LixiLan-L). In both trials, LixiLan vs. Gla-100 was associated with significantly greater reductions in A1c and PPG, no increased risk of hypoglycemia, significantly more pts achieving A1c < 7.0%, as well as the composite endpoint (A1c < 7.0% with no weight gain and no documented symptomatic hypoglycemia) (Table). The proportion of pts with gastrointestinal adverse events was higher with LixiLan than with Gla-100 (Table), but lower than with lixisenatide (data not shown). Outcomes for elderly pts were similar to those for pts aged < 65 years, although LixiLan led to modest weight loss in elderly pts in LixiLan-L (*P* = 0.007) and LixiLan-O (*P* = 0.017). Compared with Gla-100, which mainly targets FPG, the complementary actions of LixiLan on PPG and FPG improved glycemic control with no increased risk of hypoglycemia in the elderly.

Table. Efficacy and Safety of LixiLan in Pts Aged ≥ 65 Years Included in the LixiLan-O and LixiLan-L Phase 3 Clinical Trials (mITT Population for Efficacy Outcomes, Safety Population for Adverse Events).

Outcome		**LixiLan-O[a]**			**LixLan-L[b]**		
		LixiLan	**Gla-100**	**Treatment difference (SE), *P* value**	**LixiLan**	**Gla-100**	**Treatment difference (SE), *P* value**
Age at baseline (years), mean (SD)[c]		n = 113 68.8 (3.8)	n = 114 70.0 (3.9)	–1.2 (0.85) 0.167	n = 110 70.5 (5.0)	n = 119 69.6 (3.9)	0.9 (0.8) 0.270
A1c%, mean (SD)[c]	Baseline	n = 132 7.96 (0.67)	n = 114 8.05 (0.67)	–0.09 (0.09) 0.334	n = 110 8.07 (0.66)	n = 118 8.09 (0.71)	–0.02 (0.09) 0.846
	Change at Week 30	n = 132 –1.45 (0.86)	n = 114 –1.15 (0.79)	–0.30 (0.11) 0.007	n = 110 –1.11 (0.89)	n = 118 –0.48 (0.84)	–0.63 (0.12) < 0.001
	Week 30	n = 132 6.51 (0.72)	n = 114 6.90 (0.73)	–0.39 (0.10) < 0.001	n = 110 6.96 (0.88)	n = 118 7.61 (0.89)	-0.65 (0.12) < 0.001
FPG (mg/dL), mean (SD)[c]	Baseline	n = 132 181.3 (43.4)	n = 114 179.8 (40.2	1.4 (5.2) 0.784	n = 110 132.1 (32.8)	n = 118 138.6 (44.0)	–6.3 (4.9) 0.182
	Change at Week 30	n = 132 –62.7 (43.2)	n = 114 –65.2 (48.5)	2.3 (6.1) 0.709	n = 110 –8.5 (42.0)	n = 118 –17.8 (48.5)	9.4 (6.5) 0.143
PPG[d] (mg/dL), mean (SD)[c]	Baseline	n = 123 284.9 (64.9)	n = 107 278.9 (71.4)	5.8 (8.5) 0.491	n = 98 275.6 (69.7)	n = 115 270.5 (67.9)	5.2 (9.2) 0.574
	Change at Week 30	n = 123 –113.0 (78.92)	n = 107 –64.1 (70.1)	–48.8 (9.4) < 0.001	n = 98 –94.4 (87.6)	n = 115 –24.1 (70.3)	–70.3 (10.8) < 0.001
Weight (kg), mean (SD)[c]	Baseline	n = 132 87.2 (15.8)	n = 114 84.6 (15.0)	2.6 (2.1) 0.219	n = 110 84.0 (12.1)	n = 119 85.8 (14.1)	–1.8 (1.9) 0.341
	Change at Week 30	n = 132 –0.9 (3.7)	n = 114 1.2 (3.0)	–2.2 (0.5) < 0.001	n = 110 –1.2 (2.8)	n = 119 0.6 (2.5)	–1.8 (0.4) < 0.001
Proportion of pts with A1c ≤ 7.0% at Week 30, %[c]		n = 132 78.0	n = 114 54.4	24.3 (5.8) < 0.001	n = 110 51.8	n = 119 21.0	28.6 (6.0) < 0.001
Documented (SMPG ≤ 70 mg/dL) symptomatic hypoglycemia:							
Proportion of pts with events, %[e]		n = 133 27.8	n = 114 28.9	–0.9 (5.8) 0.876	n = 110 36.4	n = 119 43.7	–6.7 (6.4) 0.291
Number of events per pt-year[f]		n = 133 1.42	n=114 1.89	–0.46 (0.22) 0.035	n = 110 2.84	n = 118 4.91	–2.07 (0.35) <0.001
Proportion of pts with A1c < 7.0%, no weight gain at Week 30 and no documented hypoglycemia (SMPG ≤ 70 mg/dL), %[e]		n = 133 30.1	n = 114 14.0	16.0 (5.1) 0.002	n = 110 26.4	n = 119 8.4	17.2 (4.8) <0.001
Proportion of pts experiencing:							
Nausea, %[e]		n = 133 12.0	n = 114 2.6	9.4 (3.3)	n = 110 13.6	n = 119 0.8	12.8 (3.6)
Vomiting, %[e]		n = 133 4.5	n = 114 1.8	3.0 (2.4)	n = 110 3.6	n = 119 0.8	2.9 (2.3)

[a]Pts on Metformin. [b]Pts on ± Metformin. [c]2-way ANOVA means model for comparisons between LixiLan and Gla-100 by subgroup and for treatment by factor interaction tests. [d]Measured 2 hours after a standard liquid meal. [e]Cochran-Mantel-Haenszel test across randomization strata per protocol for comparisons between LixiLan and Gla-100 by subgroup and z-tests for treatment by factor interactions. [f]Mean rates of hypoglycemia events were compared between LixiLan and Gla-100 based on a Poisson distribution of events. mITT, modified intent to treat using last observation carried forward for pts with baseline and follow-up assessments; SMPG, Self-Measured Plasma Glucose, SD, standard deviation; SE, standard error.

Supported By: Sanofi U.S.

955-P

The Extended Duration Single Dose Pharmacokinetics (PK) and Pharmacodynamics (PD) of AB101, a Potential Once-Weekly Basal Subcutaneous (SC) Insulin, in Diabetic Miniature Swine

BRIAN K. ROBERTS, XUEYAN WANG, MARY S. ROSENDAHL, SANKARAM MANTRIPRAGADA, *Louisville, CO*

Ultra long-acting basal insulins may lead to improved glycemic control with less weight gain and fewer injections, thereby optimizing initiation of

For author disclosure information, see page A696.

and adherence to an insulin regimen. AB101 is a microsphere formulation (MS-form) of a 5 KDa PEGylated human recombinant insulin (peginsulin) and is being developed as a once weekly basal insulin. We previously reported results showing that the in vitro pharmacology of this peginsulin is comparable to native insulin, while the MS-form administered SC resulted in a slow onset and sustained increase in insulin levels with glucose reduction over an extended 5 to 10 day period in normal rats and dogs. Due to similarities in anatomy and metabolism, pigs are a useful animal model for the study of human diabetes, and are highly predictive of the SC absorption PK and pharmacology of potential therapies (Larsen and Rolin, 2004; Lin et al, 1998). Presently, we report the PK and PD of AB101 administered as a single SC dose (7 mg/kg) to alloxan-induced diabetic Yucatan miniature swine (n=4) not controlled on an existing insulin regimen (baseline glucose 276 ± 47 mg/dL). Fasting peginsulin (ELISA) and glucose (glucometer) were measured at baseline and repeatedly over a 14 day period after dosing. Results demonstrated a slow onset and sustained increase in peginsulin, and corresponding sustained glucose reductions to near normal levels over a duration of ~ 1 week. Concomitant to the onset and duration of action of AB101, background insulin was able to be weaned off. AB101 was safe and well-tolerated. In summary, in a human relevant diabetes model at clinically applicable doses, AB101 produced sustained insulin increases without acute release, and clinically significant glucose lowering over the extended period of the study, making it feasible to administer AB101 as a weekly SC basal insulin in patients with diabetes mellitus. Clinical trials of AB101 are planned.

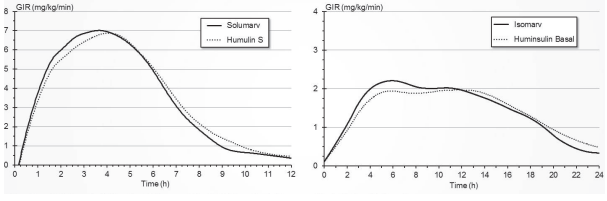
956-P

Solumarv (SOLU), a Regular Human Insulin, and Isomarv (ISO), a NPH-Insulin Preparation, Show Bioequivalence (BE) to EU-Marketed Insulins

SUSANNE FAMULLA, ULRIKE HÖVELMANN, LESZEK NOSEK, HOSS A. DOWLAT, AMEE MEHTA, TIM HEISE, *Neuss, Germany, Freiburg, Germany, Harrow, United Kingdom*

We compared the pharmacodynamics (PD) and pharmacokinetics (PK) of SOLU and ISO with those of the EU-marketed insulins Humulin S (HUM-S) and Huminsulin Basal (HUM-B), respectively. In two randomized, double blind, two way crossover studies, 26 healthy subjects (SOLU) and 55 type 1 diabetes patients (ISO) received either 0.3 U/kg SOLU or 0.6 U/kg ISO and the same dose of the comparator under clamp conditions using ClampArt, a modern automated glucose clamp device (glucose target 100 mg/dl, clamp duration 12 h (SOLU) or 24 h (ISO)). Both SOLU and ISO had similar glucose infusion rate (GIR)-profiles as their comparators (Figure). SOLU showed BE to HUM-S for both PK (insulin (INS) concentrations) and PD (treatment ratios [90% (PK)/95% (PD) [CI)]: $AUC_{INS,\ 0\text{-}12h}$ 1.015 [0.975;1.056]; INS_{max} 1.104 [0.991;1.230]; $AUC_{GIR,\ 0\text{-}12h}$ 0.996 [0.906;1.093], GIR_{max} 1.015 [0.933;1.105)]. Because of this BE only PK-BE had to be, and was, demonstrated for ISO and HUM-B according to EU-guidelines ($AUC_{INS,\ 0\text{-}24h}$ 1.039 [0.958;1.126]; INS_{max} 1.036 [0.950;1.130)]. Primary PD-endpoints also showed treatment ratios within the required range [0.80 - 1.25] for BE ($AUC_{GIR,\ 0\text{-}24h}$ 1.141 [0.946;1.376]; GIR_{max} 1.099 [0.946;1.277)]. Excellent clamp quality was demonstrated by mean deviations from target <1.1 mg/dl. In conclusion, both SOLU and ISO are bioequivalent to EU-marketed comparator insulins.

Figure. Mean LOESS-smoothed GIR-profiles of Solumarv and Humulin S (Left Panel) and Isomarv and Huminsulin Basal (Right Panel).



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957-P

Usefulness of Insulin Degludec in Older Patients with Type 2 Diabetes Poorly Controlled by Previous Insulin Therapy

MAMI YOSHIDA, ERIKO OH, HIROE KIMATA, NAOMUNE YAMAMOTO, AKIO SAEKI, MASAKAZU SUGINO, SHIGERU YOSHIDA, TAKESHI KUZUYA, NAKAAKI OHSAWA, HIROYUKI SANO, TOSHIAKI HANAFUSA, *Ibaraki City, Japan, Otsu, Japan, Takatsuki, Japan*

Purpose: In the treatment of older patients with type 2 diabetes, both maintaining relatively good glycemic control and avoiding hypoglycemia are important, but it is not easy by previous insulin regimens. This study assessed the efficacy of insulin degludec (IDeg) with ultra-long duration of action, in older patients with type 2 diabetes poorly controlled by previous insulin therapy.

Subjects and Methods: We studied 52 (male 24/female 28) out-patients with 65 years or older, whose HbA1c was over 7.0% or higher by the treatment with previous insulin for 6 months, The age of the subjects was 76.5±8.27 (mean±SD) years; the duration of diabetes 14.5±7.0 years; HbA1c 8.1±0.9%; total insulin 29±21 Units; Basal-bolus (n=24), 50Mix 3 times (n=15), 30Mix twice (n=1), BOT (n=12). We changed the basal insulin to IDeg for 1 year and examined BMI, HbA1c, FPG, 2-hour postprandial PG, standard deviation of 7 days self-measured FBS, hypoglycemia, serum HDL/LDL level, TG, prescribed dose of insulin, and QoL scores using ITR-QoL (Insulin Therapy Related QoL) and DTSQ (Diabetes Treatment Satisfaction Questionnaire).

Results: One year after the start of IDeg treatment, HbA1c, FPG, postprandial PG, the standard deviation of FBS were significantly decreased from 8.1±0.9 to 7.2±0.6%, 144±23 to 126±19 mg/dl, 232±42 to 190±25 mg/dl, 22.6±9.4 to 8.5±2.5 (p<0.01), respectively. Hypoglycemia associated with symptoms was significantly decreased from 0.3±0.83 to 0.0±0.11 times/month (p=0.047). No significant change was seen in BMI, LDL, or HDL, but TG was significantly decreased from 144±51 to 122±40mg/dl (p<0.01). The IDeg dose was significantly increased from 15.0±8.9 to 15.7±8.9 Units, but no significant change was seen in total insulin dosage. The QoL scores were significantly increased in the treatment satisfaction scores (from 5.3±0.9 to 5.6±0.8 and from 5.4±0.8 to 5.7±0.6, p<0.05).

Conclusion: Insulin Degludec was suggested to be useful in older patients with type 2 diabetes.

958-P

Clinical Outcomes of T2D Treatment Intensification Options vs. No Intensification in Patients on Basal Insulin Treatment Not Meeting A1c Goals

PHILIP LEVIN, TAO FAN, STEVE ZHOU, XUE SONG, DAMION NERO, BRIAN DAVIS, BONG-CHUL CHU, *Baltimore, MD, Bridgewater, NJ, Ann Arbor, MI*

The lack of clinical evidence to guide the most appropriate next steps for the major intensification options in T2D treatment may lead to clinical inertia. This retrospective U.S. claims data study compares the clinical outcomes of various intensification options to no intensification.

Patients with T2D and poor glycemic control after ≥6 months of basal insulin initiation were extracted from the MarketScan Commercial, Medicare and Laboratory healthcare claims databases (Jan 2005-Dec 2014). Patients intensifying with glucagon-like peptide-1 receptor agonists (GLP-1 RA), rapid-acting insulin (RAI) or an increased dose of basal insulin (>10%), within 6 months of the index date (A1c ≥ 8% if age ≥ 65 or when evidence of a comorbid condition; A1c ≥7% otherwise), were compared with those who did not intensify. Change in A1c from the index date and risk of hypoglycemia were measured 12 months following the intensification date; comparisons were made between patient cohorts using linear regression and binary logistic regression, respectively.

Among patients with a follow-up A1c measure, compared with patients not intensifying (n = 5,563) those intensifying with GLP-1 RAs (n = 257) showed the largest reduction in A1c (β: −0.346, P = 0.001) at 12 months, followed by the RAI group (n = 1,728; β: −0.098, P = 0.033), and increased basal insulin dose group (n = 3,367; β: −0.045; P = 0.199). Hypoglycemia, which was measured for all patients, followed the opposite trend; patients intensifying with GLP-1 RAs had a 43% lower risk of hypoglycemia (n = 331; odds ratio [OR]: 0.57; 95% confidence interval [95% CI]: 0.34, 0.94; P = 0.027), whereas the RAI group had a 16% increased risk (n = 2,076; OR: 1.16; 95% CI: 0.99, 1.36; P = 0.073;), and the increased basal dose group had a 29% increased risk (n = 4,134; OR: 1.29; 95% CI: 1.14, 1.46; P < 0.001).

These data may assist health care providers in choosing appropriate intensification when patients are not reaching A1c targets on basal insulin.

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959-P

Clinical Practice Gaps on Insulin Use in Diabetes Management

AMY LARKIN, JESS DROPKIN, ANNE LE, *Lexington, KY, New York, NY*

Efficient glucose control is essential to preventing life-threatening complications of diabetes, but most patients with type 2 diabetes (T2D) do not sustain long-term, adequate control. Currently, many basal insulin products are emerging and in development. We sought to assess educational and practice-related gaps related to insulin use in practice of diabetologists/endocrinologists (diab/endos) and primary care physicians (PCPs).

A survey instrument that included knowledge- and case-based, multiple choice questions was made available online during 2015 to healthcare providers without monetary compensation or charge. Respondent confidentiality was maintained and responses were de-identified and aggregated prior to analyses.

When presented with questions related to insulin in the treatment of diabetes, physicians demonstrated gaps in the following areas:

Table.

	Incorrect answer	
Topic	PCPs (n = 350)	Diab/Endos (n = 235)
Average percent of patients meeting ADA goal of A1c <7%	75%	67%
Recognizing PK/PD profile of traditional basal insulin (determir)	73%	80%
Recognizing characteristics of a new basal insulin (degludec)	53%	31%
Identifying appropriate clinical use of U-500 insulin in a patient case	82%	72%
Transitioning a patient from U-100 to U-500 insulin	58%	47%
Comparing PK/PD of glargine U-100 to glargine U-300	66%	55%
Recognizing status in development of emerging basal insulins (BIL)	68%	55%
Identifying requirements for approval of biosimilar insulins	46%	38%

With the goal of improving physician practices and patient care, this assessment of clinical practices identified knowledge and competency gaps among PCPs and diab/endos in several key areas related to insulin use. Future education is needed to close these gaps to optimize physician practices in diabetes management.

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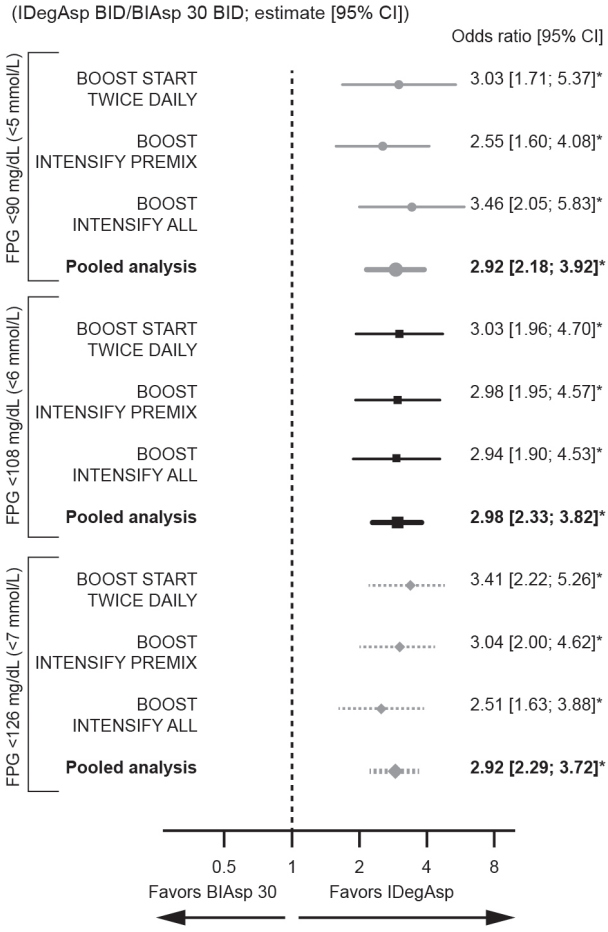
960-P

Reaching Individualized FPG Targets without Nocturnal Hypoglycemia with IDegAsp BID vs. BIAsp 30: A Meta-analysis

CHRISTOPHER H. SORLI, GREGORY FULCHER, ROOPA MEHTA, SØREN LINDBERG, LARS BARDTRUM, STEPHEN C. BAIN, *Billings, MT, Sydney, Australia, Mexico City, Mexico, Virum, Denmark, Søborg, Denmark, Swansea, United Kingdom*

ADA/EASD 2015 guidelines recommend personalized glycemic targets to balance benefits and risks (e.g., hypoglycemia) in individual patients. Assessing the likelihood of reaching glycemic targets without nocturnal hypoglycemia with different therapies may aid achievement of individualized targets. The proportion of patients reaching fasting plasma glucose (FPG) targets (<90 mg/dL, <108 mg/dL or <126 mg/dL) without nocturnal hypoglycemia (00:01-05:59 h inclusive) during the maintenance period (last 12 weeks of treatment) was assessed using data pooled from three 26-week, treat-to-target phase 3a/b trials of IDegAsp (a novel co-formulation of 70% insulin degludec [IDeg] and 30% insulin aspart [IAsp]) twice daily (BID) vs. biphasic IAsp 30/70 (BIAsp 30) BID in the IDegAsp clinical development program (BOOST). Patients were insulin naïve (BOOST START TWICE DAILY) or switched from basal or pre-mix insulin (BOOST INTENSIFY PREMIX I or INTENSIFY ALL). End-of-trial A1c did not differ between IDegAsp and BIAsp 30 in the 3 trials. Patients were significantly more likely to reach all FPG targets without nocturnal hypoglycemia with IDegAsp vs. BIAsp 30: the odds ratio ranged from 2.92 to 2.98 for all 3 FPG targets ($p<0.0001$ for all analyses) (Figure 1). Treatment with IDegAsp BID vs. BIAsp 30 BID may help achieve personalized FPG targets without nocturnal hypoglycemia for a wide range of patients with T2D.

Figure 1. Treatment Odds Ratios for Patients Achieving FPG Targets without Nocturnal Hypoglycemia.



*$p<0.0001$. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart.

Supported By: Novo Nordisk Inc.

961-P

Factors Influencing Continuation of Insulin Therapy in Patients with Diabetes Mellitus Type 2 at Hospital Discharge

JULIA K. MADER, KLAUS DONSA, KATHARINA M. NEUBAUER, FELIX ABERER, LUKAS SCHAUPP, HARALD SOURIJ, STEPHAN SPAT, BERNHARD HOELL, PETER BECK, THOMAS R. PIEBER, JOHANNES PLANK, *Graz, Austria*

Current guidelines recommend the use of clinical decision support systems to achieve glycemic control in hospitalized patients and to establish individualized discharge plans. The aim of this analysis was to determine which factors are influencing continuation of insulin therapy in patients with diabetes mellitus type 2 (T2D) at hospital discharge. 51 T2D patients without preexisting insulin therapy were treated with basal-bolus insulin therapy using GlucoTab®, a decision support system for glycemic management in hospital, during their inpatient stay. In 26 (13 female, age 72 ± 12 years, A1c 69 ± 27 mmol/mol, BMI 31 ± 8 kg/m^2, diabetes duration 11 ± 10 years) patients insulin therapy was terminated at discharge (NoIns group), in 25 (8 female, age 65 ± 10 years, A1c 83 ± 27 mmol/mol, BMI 27 ± 4 kg/m^2, diabetes duration 9 ± 8 years) patients insulin therapy was recommended to be continued at home (Ins group) based on the judgment of the diabetes specialist in charge. Mean BG was lower for NoIns prior to (206 ± 76 vs. 230 ± 87 mg/dL) and during GlucoTab® treatment (143 ± 34 vs. 159 ± 29 mg/dL). BG in the range 70-180 mg/dL was greater (79.7 vs. 68.6%), while rates of hypoglycemia <70 mg/dL were similar (1.4 vs. 1.9%, NoIns vs. Ins, respectively). In neither group a BG value <40 mg/dL was observed. Total daily insulin dose was lower in the NoIns group (37 ± 15 vs. 46 ± 10 U). Duration of GlucoTab® treatment during hospital stay (7.4 ± 4.2 vs. 7.5 ± 4.0 days) and acute admission rates (81 vs. 88%) were similar between groups (NoIns vs. Ins, respectively).

For author disclosure information, see page A696.

In a logistic regression analysis age <70 years and A1c ≥60 mmol/mol were predictive factors for continuation of insulin therapy after discharge, p<0.05. Incorporation of factors influencing insulin therapy at discharge in a decision support system for inpatient glycemic management might help to facilitate the discharge process by timely initiation of patient education.

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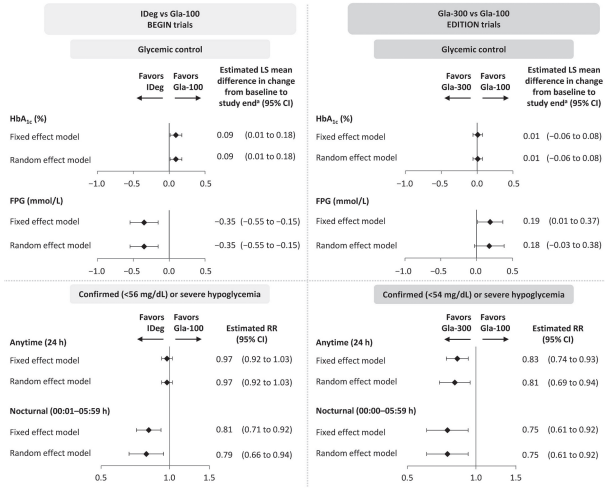
962-P

Clinical Perspectives from the BEGIN and EDITION Longer-Acting Insulin Programs: Trial-Level Meta-analyses Outcomes with either Degludec (IDeg) or Glargine 300 U/mL (Gla-300) vs. Glargine 100 U/mL (Gla-100) in T2DM

JULIO ROSENSTOCK, ROBERT A. RITZEL, SOAZIG CHEVALIER, BEVERLEY BALKAU, RONAN ROUSSEL, *Dallas, TX, Munich, Germany, Chilly Mazarin, France, Villejuif, France, Paris, France*

Efficacy and safety of IDeg and Gla-300 were compared with Gla-100 in the BEGIN and EDITION programs, respectively. HbA_{1c}, FPG and hypoglycemia incidence with IDeg or Gla-300 vs. Gla-100 were explored in 2 trial-level metaanalyses of clinical trials in T2DM (Figure). FPG reduction was significantly more pronounced with IDeg vs. Gla-100 but HbA_{1c} reduction was significantly greater for Gla-100. HbA_{1c} reduction was comparable with Gla-300 and Gla-100 whereas FPG reduction was significantly greater with Gla-100 in the fixed but not random effect model. Risk of ≥1 confirmed (<56 mg/dL) or severe hypoglycemic event was lower with IDeg vs. Gla-100 at night (00:01-05:59 h) but comparable at any time (24 h). Risk of ≥1 confirmed (<54 mg/dL) or severe hypoglycemic event was lower with Gla-300 vs. Gla-100 at night (00:00-05:59 h) and also at any time (24 h). Risk of ≥1 severe hypoglycemic event was comparable with IDeg or Gla-300 vs. Gla-100. Summary, in trial-level metaanalyses in T2DM, Gla-100 reduced HbA_{1c} more than IDeg despite IDeg having a greater FPG-lowering effect. Hypoglycemia risk was lower with IDeg vs. Gla-100 for nocturnal but not anytime events. Gla-300 provided comparable glycemic control to Gla-100 with lower risk of anytime and nocturnal hypoglycemia. Head-to-head trials of IDeg vs. Gla-300 are needed.

Figure. Estimated LS Mean Differences in HbA_{1c} and FPG, and Relative Risk of ≥1 Hypoglycemic Event, in T2DM†: Two Trial-level Metaanalyses of Data from IDeg vs. Gla-100 and Gla-300 vs. Gla-100 Clinical Trials.



†T2DM analysis pool includes studies: Five BEGIN studies (IDeg vs Gla-100): NCT00972283 (52 weeks, basal-bolus), NCT00982644 (52 weeks, insulin-naive), NCT01068665 (26 weeks, insulin-naive), NCT01006291 (26 weeks, insulin-naive or basal ± OADs), NCT01059799 (26 weeks, insulin-naive); Four EDITION studies (Gla-300 vs Gla-100): NCT01499082 (26 weeks, basal + mealtime insulin), NCT01499095 (26 weeks, basal insulin + OADs), NCT01676220 (26 weeks, insulin-naive), NCT01689142 (26 weeks, basal insulin + OADs). Study durations selected based on time of primary endpoint. No significant heterogeneity of treatment effect across studies was observed (p>0.05). *LOCF analysis was used for the BEGIN studies and MMRM analysis was used for the EDITION studies except for FPG data in NCT01689142, for which LOCF analysis was used.

Supported By: Sanofi

963-P

Accurate Assessment of Beta-Cell Function in Patients Treated with CSII

YING TAN, WEN XU, CHUNMIAO WEN, SIHUI LUO, JINHUA YAN, MENGYIN CAI, BIN YAO, JIANPING WENG, *Guangzhou, China*

During treatment with continuous subcutaneous insulin infusion (CSII), endogenous insulin secretion maximally decrease because of the "β-cell rest" effect. Thus, assessment of β-cell function during CSII may not reflect the real status of β-cell function. This study was designed to evaluate the impact of CSII on β-cell function assessment.

Patients with T2DM admitted to our hospital treated with CSII were enrolled. C-peptide levels (0 min, 30 mins and 120 mins after a mixed meal) were measured before CSII started. When patients achieved the target of fasting capillary glucose ≤7.0mmol/L, C-peptide levels (0 min, 30 mins and 120 mins after a mixed meal) were measured. Then CSII were stopped at 10 pm with the same tests repeated on the next day.

125 patients who were 51.9±11.7 years old with diabetic duration 12.0 (1, 72) years, BMI 24.5±3.7Kg/$m^2$and HbA1c 10.5±2.5% achieved the glycemic target in 6.0±3.3 days. C-peptide levels before and after CSII were shown in Table 1. Compared with those measured before CSII, C-peptide levels before stopping CSII at all time points decreased even glucose control was achieved, but significantly increased immediately after CSII was stopped. The C-peptide after stopping CSII increased to 141% (0 min), 127% (30 mins) and 219% (120 mins), respectively, compared to those before stopping CSII.

CSII therapy should be stopped for accurate evaluation of β-cell function due to its "β-cell rest" effect in T2DM.

Table 1. C-peptide Levels (nmol/L) Before and After CSII During a Mixed Meal.

	0 min	30 mins	120 mins
Before CSII treatment	0.35±0.20	0.57±0.31	0.84±0.54
Before stopping CSII	0.23±0.13*	0.39±0.26*	0.67±0.50*
After stopping CSII	0.41±0.16*#	0.71±0.33*#	1.37±0.75*#

Data are mean±SD. *P<0.05 compared to the C-peptide level before CSII treatment, #P<0.05 compared to the C-peptide level before stopping CSII treatment.

964-P

Similar Efficacy and Safety of LY2963016 Insulin Glargine and Insulin Glargine (Lantus®) in Patients with T2D in Age Groups (<65 Yrs, =65 Yrs)

ROBYN K. POLLOM, TIMOTHY COSTIGAN, LYNDON B. LACAYA, LIZA L. ILAG, PRISCILLA A. HOLLANDER, *Indianapolis, IN, Dallas, TX*

The ELEMENT-2 phase 3, randomized, double-blind, 24-week study in patients with type 2 diabetes (T2D) showed that LY2963016 insulin glargine (LY IGlar) has a similar efficacy and safety profile to insulin glargine (Lantus®; IGlar). To further characterize the similarity of LY IGlar to IGlar, products with identical amino acid sequences, subgroup analyses compared LY IGlar and IGlar in patients from ELEMENT-2 based on age at study entry (≥65 yrs, <65 yrs). At baseline, patients ≥65 yrs (N=214) had significantly (p<.05) longer diabetes duration, lower baseline A1c, body weight, and body mass index, and higher percentage reporting prestudy IGlar use than those <65 yrs (N=542). No significant treatment-by-age interactions (p≥.05) were observed for any of the clinical efficacy and safety outcomes (Table), including incidence (p=.459) and rate of documented symptomatic hypoglycemia (p=.769), incidence of treatment-emergent adverse events (p=.714), serious adverse events (p=.487), and insulin antibodies (% binding, p=.331), indicating no significant differential treatment effect between LY IGlar and IGlar across both age groups. Moreover, no treatment differences (p≥.05) were observed within each age group for any of the clinical efficacy and safety outcomes. In conclusion, LY IGlar and IGlar exhibit similar efficacy and safety in elderly patients with T2D.

Table.

Outcome LSM (SE) unless otherwise indicated		≥65 years		<65 years		INT p-value[b]
		LY IGlar (N=112)[a]	IGlar (N=102)[a]	LY IGlar (N=264)[a]	IGlar (N=278)[a]	
A1c (%)	Change from baseline (Week 24 LOCF)	-1.307 (0.09)	-1.279 (0.09)	-1.280 (0.07)	-1.363 (0.07)	0.429
	LSM diff [95% CI] (Week 24 LOCF)	-0.028 [-0.260, 0.205]		0.083 [-0.062, 0.229]		
Daily Mean Blood Glucose (mg/dL)	Change from baseline (Week 24 LOCF)	-37.358 (4.48)	-34.570 (4.61)	-40.529 (3.44)	-42.908 (3.42)	0.433
	LSM diff [95% CI] (Week 24 LOCF)	-2.788 [-13.724, 8.148]		2.379 [-4.335, 9.092]		
FBG (mg/dL) by SMBG	Change from baseline (Week 24 LOCF)	-44.057 (4.55)	-39.628 (4.62)	-49.482 (3.37)	-49.294 (3.37)	0.534
	LSM diff [95% CI] (Week 24 LOCF)	-4.428 [-15.763, 6.906]		-0.187 [-7.188, 6.813]		
Basal Insulin Dose (U/kg/day)	Change from baseline (Week 24 LOCF)	0.292 (0.037)	0.293 (0.038)	0.396 (0.028)	0.400 (0.028)	0.951
	LSM diff [95% CI] (Week 24 LOCF)	-0.001 [-0.092, 0.091]		-0.004 [-0.061, 0.054]		
Weight (kg)	Change from baseline (Week 24 LOCF)	1.412 (0.372)	1.397 (0.382)	1.978 (0.281)	2.298 (0.279)	0.553
	LSM diff [95% CI] (Week 24 LOCF)	0.015 [-0.920, 0.951]		-0.320 [-0.905, 0.264]		
Total hypoglycemia rate (events/pt/30 days), Overall	Negative binomial mean (SE)	2.13 (0.25)	2.16 (0.26)	1.60 (0.13)	1.74 (0.14)	0.737
	Odds ratio[c] [95% CI]	0.99 [0.71, 1.37]		0.92 [0.73, 1.15]		
Nocturnal hypoglycemia rate (events/pt/30 days), Overall	Negative binomial mean (SE)	0.76 (0.12)	0.68 (0.11)	0.56 (0.06)	0.67 (0.07)	0.310
	Odds ratio[c] [95% CI]	1.11 [0.72, 1.72]		0.84 [0.61, 1.14]		
N (%) of Patients Reaching A1c <7.0%		55 (50.0)	55 (53.9)	125 (48.3)	142 (52.0)	0.983[d]
Total Hypoglycemia Incidence, N (%), Overall		95 (85.6)	81 (80.2)	201 (76.7)	211 (76.7)	0.362[d]
Nocturnal Hypoglycemia Incidence, N (%), Overall		72 (64.9)	58 (57.4)	140 (53.4)	145 (52.7)	0.389[d]
N (%) of Patients with TEAR,Overall		3 (2.8)	1 (1.0)	11 (4.3)	13 (4.9)	0.334[d]

[a]N reflects the total number of patients within each age subgroup (≥65 yrs, <65 yrs) and treatment (LY IGlar, IGlar) from the Full Analysis Set.
[b]Within subgroup p-values >0.05; [c]Odds ratio (LY IGlar negative binomial mean/IGlar negative binomial mean) from negative binomial regression model; [d]Homogeneity of odds ratios across subgroups was assessed using the Breslow Day test.
Overall is at any time during the postrandomization visits; data are from NCT01421459.
Hypoglycemia was defined as blood glucose ≤70 mg/dL or signs or symptoms of hypoglycemia.
TEAR was defined as having %antibody binding of at least 1.26% if with nondetectable antibodies at baseline; or >1% (absolute) AND 30% (relative) above baseline values if with detectable antibodies at baseline.
Abbreviations: CI=confidence interval; diff=difference; FBG=fasting blood glucose; IGlar=insulin glargine; INT=interaction; LOCF=last-observation carried forward; LSM=least squares mean; LY IGlar=LY2963016 insulin glargine; SE=standard error; SMBG=self-monitored blood glucose; TEAR=treatment-emergent antibody response.

Supported By: Eli Lilly and Company and Boehringer Ingelheim

965-P

Efficacy of Insulin Glargine/Lixisenatide Fixed-Ratio Combination in Patients with T2D According to Health Care Effectiveness Data and Information Set (HEDIS) Measures

DANNY H. SUGIMOTO, TERRY DEX, WILLIAM STAGER, CHRISTINE YU, VANITA R. ARODA, *Chicago, IL, Bridgewater, NJ, Hyattsville, MD*

HEDIS measures from the U.S. National Committee for Quality Assurance provide indicators for individualized diabetes care. The efficacy of once-daily LixiLan, a titratable fixed-ratio combination of insulin glargine 100 U/mL (Gla-100) and lixisenatide currently in development, was investigated in two 30-week phase 3 clinical trials: LixiLan-O in patients (pts) with T2D uncontrolled on Metformin (MET) ± oral antidiabetes drugs (OADs), and LixiLan-L in pts with T2D uncontrolled on basal insulin ± OADs. In this post-hoc analysis, pts from both trials were stratified based on HEDIS criteria into low risk (LR; pts < 65 years and no HEDIS-defined comorbidities) or high risk (HR; pts ≥ 65 years or with HEDIS-defined comorbidities) groups, with HEDIS-defined A1c goals < 7.0% and < 8.0%, respectively. HR pts were older and had a longer diabetes duration in both trials vs. LR pts (Table). LixiLan was consistently more effective in lowering A1c in both HR and LR groups, and allowed more pts to achieve HEDIS-defined A1c goals in both trials, compared to those on Gla-100 or lixisenatide (Table). LixiLan, which targets both fasting and postprandial plasma glucose, improved A1c levels in both HEDIS-defined subgroups for diabetes care, in pts insufficiently controlled on MET ± OAD, or on basal insulin ± OADs, compared with Gla-100 and lixisenatide alone.

Table. Efficacy of LixiLan in LR and HR Pts in LixiLan-O and LixiLan-L Phase 3 Clinical Trials (mITT Population).

	LixiLan-O[a]						LixiLan-L[b]			
	LixiLan		Gla-100		Lixisenatide		LixiLan		Gla-100	
	LR n=295	HR n=173	LR n=303	HR n=163	LR n=153	HR n=80	LR n=215	HR n=151	LR n=215	HR n=150
Age (years), mean (SD)	53.6 (7.8)	66.2 (6.3)	54.0 (7.5)	66.5 (6.9)	54.5 (6.7)	66.6 (6.0)	54.5 (6.7)	67.0 (7.7)	55.5 (6.5)	67.2 (6.3)
Diabetes duration (years), mean (SD)	8.3 (5.3)	9.9 (5.7)	7.3 (4.6)	11.2 (6.4)	7.8 (4.6)	10.8 (8.3)	10.6 (5.7)	14.2 (7.3)	10.7 (6.5)	14.1 (6.9)
FPG baseline (mg/dL), mean (SD)	176.2 (42.4)	180.7 (42.1)	175.1 (43.5)	176.9 (39.0)	176.3 (41.2)	176.6 (34.4)	129.1 (34.6)	136.0 (35.2)	127.9 (33.6)	137.8 (41.5)
A1c baseline (%), mean (SD)	8.14 (0.72)	7.97 (0.68)	8.10 (0.70)	8.03 (0.68)	8.17 (0.75)	8.07 (0.66)	8.08 (0.72)	8.05 (0.64)	8.05 (0.74)	8.11 (0.71)
A1c at Week 30 (%), mean (SD)	6.54 (0.79)	6.54 (0.77)	6.84‡ (0.81)	6.85‡ (0.72)	7.41δ (0.90)	7.21δ (0.85)	6.98 (0.92)	6.98 (0.84)	7.46‡ (0.93)	7.54‡ (0.88)
A1c change (%), mean (SD)	–1.60 (0.89)	–1.43 0.86)	–1.27‡ (0.90)	–1.18* (0.80)	–0.76δ (0.85)	–0.86δ (0.90)	–1.10 (0.90)	–1.07 (0.90)	–0.60‡ (0.88)	–0.57‡ (0.85)
Proportion of pts who achieved A1c goal[c] at Week 30, %	76	94	62	93	32	83	59	89	34	70

*P < 0.05, 2-way ANOVA means model for comparisons between LixiLan and Gla-100 by subgroup and for treatment by factor interaction tests. ‡P < 0.001, 2-way ANOVA means model for comparisons between LixiLan and Gla-100 by subgroup and for treatment by factor interaction tests. δP < 0.001, 2-way ANOVA means model for comparisons between LixiLan and lixisenatide by subgroup and for treatment by factor interaction tests. [a]Pts on Metformin. [b]Pts on ± Metformin. [c]A1c goals were A1c < 7.0% for the LR population, and A1c < 8.0% for the HR population based on HEDIS measures. mITT, modified intent to treat using last observation carried forward for pts with baseline and follow-up assessments; SD, standard deviation.

Supported By: Sanofi U.S.

966-P

Noninferiority Effects on Glycemic Control and Glucose Fluctuation in Newly Diagnosed Type 2 Diabetic Patients: Glargine plus Oral Antidiabetic Agents vs. Continuous Subcutaneous Insulin Infusion Treatment

MU CHEN, SHUO LIN, WANLING CHEN, BILIAN ZHU, KEYI LIN, PANWEI MU, MANMAN WANG, WEN XU, LONGYI ZENG, *Guangzhou, China*

This study aimed to compare the effects of basal supported oral therapy using Glargine with continuous subcutaneous insulin infusion (CSII) treatment in newly diagnosed diabetic patients. In this nearly 2-week, randomized, parallel-group study, 68 newly diagnosed diabetic patients (mean age 48.3 years, with Fasting plasma glucose (FPG) ≧11.1mmol/L or HbA1c≧9%) were randomized to receive CSII (n=35) or glargine in combination with Metformin and Gliclazide (n=33). Glycated albumin (GA) and HbA1c were measured at baseline and at the end of the study. All subjects completed a 3-day period of glucose monitoring using CGMS after patients achieving the glucose target (FPG<7.0mmol/L, 2hBG<10mmol/L) for 3-5 days. Most subjects achieved glucose target in 3-5 days. Mean time for treatment in CSII and glargine group were 10.5 and 10.6 days, respectively (P>0.05). There was a significant improvement in HbA1c and GA values, with mean (95% CI) HbA1c changes from baseline -0.94% (-0.44% to -1.44%) in CSII group and -0.80% (-0.45% to -1.15%) in glargine group. GA changes in CSII and glargine group were -6.44% (-3.22% to -9.22%) and -6.41% (-2.86% to -9.96%), respectively (P>0.05). No difference in the improvement of HbA1c and GA between two groups was observed (P>0.05). Mean amplitude of glycemic excursions (MAGE) in CSII group and glargine group were 3.40 and 3.16 mmol/L, respectively (P=0.484). 24-h mean blood glucose (MBG) and standard deviation of MBG (SDBG) in CSII group were 7.49 and 1.41 mmol/L, respectively, while in glargine group were 7.02 and 1.21 mmol/L. No difference in MBG and SDBG were observed between two groups (P>0.05). Both groups showed efficacy regarding glycemic control and glucose fluctuation with similar effects. Short-term glargine based oral agents therapy might be an alternative option to CSII for initial insulin therapy in newly diagnosed type 2 diabetic patients.

Supported By: Science and Technology Planning Project of Guangdong Province (013B021800198); Science and Technology Planning Project of Guangzhou City ([2014]151)

967-P

Effects of Insulin Degludec vs. Insulin Glargine on Glycemic Control and Intra-individual Day-to-Day Fasting Blood Glucose Variability in Insulin Naïve Patients with Type 2 Diabetes: I'd Got Trial

YOSHIMASA ASO, KUNIHIRO SUZUKI, YASUKO CHIBA, MINORU SATO, NOBUYA FUJITA, YOSHIHISA TAKADA, SHUNICHI MURANO, HISAMOTO KURODA, *Mibu, Japan, Ashikaga, Japan, Utsunomiya, Japan, Tochigi, Jordan, Tochigi, Japan*

Aims: Insulin degludec (IDeg) is an ultra-long acting insulin that has a smooth time-action profile of more than 42 hours. Pharmacodynamics showed the day-to-day variability with IDeg was four times lower than that of insulin glargine (IGla). We compared the effects of IDeg with IGla on change in HbA1c from baseline week 24 and intra-individual day-to-day fasting blood glucose (FBG) variability in insulin naïve patients with type 2 diabetes.

Subjects and Methods: Eligible patients were randomly allocated in a 3:1 ratio to receive once-daily IDeg (n=31) or IGla (n=12) in the morning. Insulin was titrated to a target FBG < 110 mg/dl by SMBG before breakfast. The primary endpoints were changes in HbA1c from baseline to 24 weeks and the standard deviation (SD) and coefficient of variation (CV) of FBG during 8 to 12 weeks and 20 to 24 weeks of each treatment period. Secondary endpoints included dose of insulin and QoL.

Results: After 24 weeks, HbA1c decreased by 1·6% in the IDeg group and 1·7% in the IGlag at the same doses of insulin in each treatment, showing no significant difference. FBG levels during 8-14 weeks and 20-24 weeks were significantly lower in the IDeg than in the IGla group. We found no significant differences in SD of FBG between the two groups, however, CV was significant lower in the IDeg group than in the IGla group. Rates of overall or severe hypoglycemic did not differ between groups. Anxiety and dissatisfaction with treatment improved in the IDeg group.

Conclusions: Insulin degludec showed a similar glycemic improvement to insulin glargine in insulin naïve people with type 2 diabetes. Insulin degludec may be associated with a lower FBG and smaller day-to-day variability of FBG, compared with insulin glargine.

968-P

Insulin Degludec Provides Similar Glycemic Control with Insulin Glargine in Patients with Type 2 Diabetes

SATORU YAMADA, MANAHO KOMURO, GAKU INOUE, MITSUHISA TABATA, HAJIME MATSUBARA, JUNICHIRO IRIE, *Tokyo, Japan*

Background: Previously, we reported insulin degludec provided similar glycemic control comparing with insulin glargine, with less insulin dose in type 1 diabetes, using blinded continuous glucose monitoring (CGM). In this study, we compared the glucose-lowering effects, glycemic variability, and insulin doses during treatment with insulin degludec or insulin glargine using CGM in type 2 diabetes.

Research Design and Methods: In this open-label, single-center, two-way crossover study, 18 outpatients with type 2 diabetes who were on basal-bolus insulin therapy were assigned to receive either insulin glargine followed by insulin degludec, or insulin degludec followed by insulin glargine. The basal insulin doses were fixed in principle and the patients self-adjusted their bolus insulin doses. Seventy-two-hour CGM was performed 2 weeks after switching the basal insulin.

For author disclosure information, see page A696.

Results: The mean blood glucose (mg/dL) was not significantly different between insulin degludec and insulin glargine for 48 h (141.4 ± 25.2 *vs.* 142.8 ± 23.1), at nighttime (125.2 ± 34.0 *vs.* 130.0 ± 29.1), and during daytime (148.3 ± 24.9 *vs.* 146.7 ± 25.5). The SD (mg/dL) was also similar (for 48 h: 37.7 ± 12.0 *vs.* 36.5 ± 12.7; nighttime: 14.2 ± 12.2 *vs.* 14.7 ± 11.3; daytime: 37.0 ± 10.2 *vs.* 33.9 ± 10.7). Other indices of glycemic control, glycemic variability, and hypoglycemia were similar for both insulins. The total daily insulin dose (TDD) and the total daily bolus insulin dose (TDBD) were not different between two long-acting insulins (TDD: 0.35 ± 0.13 *vs.* 0.35 ± 0.13 U/kg/day; TDBD: 0.20 ± 0.08 vs. 0.20 ± 0.08 U/kg/day).

Conclusion: Insulin degludec provides similar effective and stable glycemic control with insulin glargine in type 2 diabetes.

Supported By: Kitasato Institute Hospital

969-P

Greater Early Glucose-Lowering Effect of Faster-Acting Insulin Aspart Is Observed Consistently from Day-to-Day

LESZEK NOSEK, HANNE HAAHR, TIM HEISE, ULRIKE HÖVELMANN, LARS ERICHSEN, ERIC ZIJLSTRA, KIRSTINE STENDER-PETERSEN, *Neuss, Germany, Søborg, Denmark*

Faster-acting insulin aspart (faster aspart) is insulin aspart (IAsp) in a new formulation with faster initial absorption and greater early glucose-lowering effect. This study aimed to investigate within-subject day-to-day variability in the pharmacodynamic (PD) effect of faster aspart.

Subjects with type 1 diabetes (N=45; HbA_{1c} [± SD]: 7.4 ± 0.85%; age [± SD]: 44.0 ± 10.4 years) received three single 0.2 U/kg doses of either faster aspart (n=23) or IAsp (n=22) under automated euglycemic glucose clamp conditions (ClampArt, BG target 100 mg/dL; duration up to 12 h post-dose) on three identical study days in a double-blind, randomized fashion.

Faster aspart had a greater early PD effect, indicated by 14-27% higher glucose infusion rates (GIR) in the first 2 hours (treatment ratio [95% CI]: $AUC_{GIR,\ 0\text{-}1h}$, 1.27 [1.16; 1.40]; $AUC_{GIR,\ 0\text{-}2h}$, 1.14 [1.08; 1.21]) with low intra-individual day-to-day variability. Within-subject coefficients of variation (CV) for early glucose-lowering effects were low for faster aspart and similar to IAsp (Table), as was within-subject variability for total ($AUC_{GIR,\ 0\text{-}12h}$) and maximal (GIR_{max}) GIR (Table).

In conclusion, low day-to-day variability in PD endpoints after treatment with faster aspart is associated with a consistently high early glucose-lowering effect.

Table. Within-Subject Variability for Glucose-lowering Effect with Faster Aspart vs. IAsp.

PD (glucose-lowering effect)	CV (%)	
	Faster aspart	IAsp
Early		
$AUC_{GIR,\ 0–1h}$	25.5	21.6
$AUC_{GIR,\ 0–2h}$	20.4	17.9
Total		
$AUC_{GIR,\ 0–12h}$	18.3	18.4
GIR_{max}	19.3	21.0

Within-subject variability, as determined by CV, was calculated based on 3 single doses (0.2 U/kg) of either faster aspart or insulin aspart for the PD endpoints. The endpoint was log-transformed and analyzed using a linear mixed model with treatment as a fixed effect and subject as a random effect. AUC=area under the curve; CI=confidence interval; CV=coefficient of variation; GIR_{max}=maximum glucose infusion rate; IAsp=insulin aspart; PD=pharmacodynamics.

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970-P

Observational Study to Assess the Impact of Intensification Therapy with Basal Insulin and Lixisenatide to Achieve Glycemic Control in Real Life in Patients with Type 2 Diabetes

DIEGO BELLIDO, PABLO ABELLÁN, JOSÉ MANUEL RUIZ-PALOMAR, ROGELIO ÁLVAREZ-SINTES, ANDREU NUBIOLA, CRISTINA ARANDA, *Ferrol, Spain, Castellón de la Plana, Spain, Alicante, Spain, Pontevedra, Spain, Barcelona, Spain*

Lixisenatide, a selective glucagon-like peptide-1 receptor agonist, is indicated for the treatment of patients with type 2 diabetes in combination with oral antidiabetic drugs +/- basal insulin. We aimed to assess the effectiveness of lixisenatide + basal insulin. Cross-sectional, observational study of adult patients with type 2 diabetes poorly controlled with basal insulin who initensificated therapy with lixisenatide at least 6 months before study inclusion by physician decision, following ADA/EASD 2012 guidelines and real life conditions. 129 patients were evaluated (age, 58.7±10 yrs; men, 52.7%). After 6 months of treatment with lixisenatide + basal insulin a statistically significant change in mean HbA1c (-1.1%) and body weight (-4Kg) was achieved. The breakdown by HbA1c is shown in Table below. Significant increases in the percentage of patients achieving HbA1c ≤7% (9.3% vs. 30.2%) and ≤6.5% (3.1% vs. 17.1%) were observed. 30 (10%) patients reported 16 adverse reactions, being nausea the most frequent (9.3%). Findings from this study show significant reductions in glycemic control and ponderal parameters after 6 months of intensification therapy with lixisenatide plus basal insulin in real life conditions.

Table.

	Baseline HbA1c						TOTAL (N=129)
	< 6% (N=4)	6-7% (N=6)	7-8% (N=29)	8-9% (N=41)	9-10% (N=26)	≥ 10% (N=23)	
HbA1c (%)							
Initiation of therapy with lixisenatide	5.7±0.1	6.8±0.1	7.6±0.3	8.3±0.3	9.4±0.3	11.2±0.9	8.7±1.5
After 6 months of therapy with lixisenatide	6.0±0.8	6.8±0.5	7.0±0.7	7.6±0.9	8.0±1.0	8.4±1.7	7.6±1.2
p-value	0.472	>0.999	<0.001	<0.001	<0.001	<0.001	<0.001
FBG (mg/dl)							
Initiation of therapy with lixisenatide	96.6±18.5	116.5±15.3	152.0±35.4	163.2±41.4	190.8±56.4	238.2±63.1	175.4±58.5
After 6 months of therapy with lixisenatide	110.8±27.6	119.5±17.4	124.2±33.4	148.4±51.9	154.1±36.6	159.2±58.3	143.5±46.7
p-value	0.144	0.697	<0.005	<0.05	<0.05	<0.001	<0.001
PPG (mg/dl)							
Initiation of therapy with lixisenatide	145.0±29.0	179.3±30.1	201.5±34.8	206.0±40.3	226.8±58.9	279.0±59.5	218.9±56.2
After 6 months of therapy with lixisenatide	132.5±14.1	150.2±30.2	149.8±28.1	166.1±37.5	168.7±35.5	181.0±56.5	163.9±39.8
p-value	0.472	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001
BMI (kg/m²)							
Initiation of therapy with lixisenatide	39.9±7.1	36.0±3.6	34.1±4.2	35.1±4.7	35.9±4.5	38.2±6.0	35.8±5.0
After 6 months of therapy with lixisenatide	38.3±8.0	34.2±4.4	32.7±4.1	33.8±4.8	34.6±4.0	36.5±5.9	34.3±4.9
p-value	0.129	0.122	<0.001	<0.001	<0.005	<0.05	<0.001
Body weight (kg)							
Initiation of therapy with lixisenatide	96.5±19.8	102.8±18.8	95.3±15.0	94.8±15.6	95.0±13.0	107.1±18.7	97.6±16.3
After 6 months of therapy with lixisenatide	92.7±22.3	97.3±18.3	91.3±15.0	91.1±15.7	91.6±12.0	102.2±17.0	93.6±15.7
p-value	0.139	0.122	<0.001	<0.001	<0.005	<0.05	<0.001

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; PPG, posprandial glucose.

971-P

All-Cause Mortality Comparison of Different Insulin Regimens in T2DM Patients: A Meta-analysis

XUEYING GAO, XIAOLING CAI, WENJIA YANG, LINONG JI, *Beijing, China*

To compare the risk of all-cause mortality in T2DM patients treated with different patterns of insulin. We searched the following databases: MEDLINE, EMBASE, CENTRAL. The PubMed search strategy formed the basis for the strategies developed for other databases. References were collected until June. 2015. The main search concepts were T2DM, NPH insulin, long acting insulin analogs, human regular insulin, rapid insulin analogs, premixed insulin, premixed insulin analogs, randomized controlled trials. Inclusion criteria for studies were: type 2 diabetic patients aged >18 years; randomized controlled trials with at least 4 weeks of follow-up. All statistical analyses were conducted in the Review Manager statistical software (Version5.3). The odds ratio (OR) and 95% confidence index (CI) were provided to evaluate the all-cause mortality. A total of 71 articles were included in this review. No statistically significant difference was found in terms of all-cause mortality between NPH insulin therapy (n=4806) and long acting insulin analogs therapy (n=5813) (OR = 1.15; 95% CI: 0.61 to 2.18). No statistically significant difference was found in terms of all-cause mortality between human regular insulin therapy (n=1456) and rapid insulin analogs therapy (n=1463) (OR = 1; 95% CI: 0.20 to 4.98). Compared with premixed insulin therapy (n=349), no statistically significant difference was found in premixed insulin analogs therapy (n=313) (OR = 0.28; 95% CI: 0.03 to 2.75). Compared with premixed insulin therapy (n=3249), no statistically significant difference was found in basal insulin therapy (n=3164) (OR = 2.12; 95% CI: 0.83 to 5.38). Compared with premixed insulin therapy (n=2955), no statistically significant difference was found in basal-bolus/bolus insulin therapy (n=3146) (OR = 0.88; 95% CI: 0.44 to 1.77). From this systemic review, no statistically significant differences were found among different insulin regimens in terms of all-cause mortality in T2DM patients.

972-P

Drivers of and Barriers to Optimal Basal Insulin (BI) Titration: Results of a Quantitative Survey

LORI D. BERARD, WILLIAM H. POLONSKY, MIREILLE BONNEMAIRE, MARIE MICAL, STEVEN V. EDELMAN, KAMLESH KHUNTI, *Winnipeg, MB, Canada, Del Mar, CA, Paris, France, Leicester, United Kingdom*

An online survey of 386 healthcare professionals (HCPs) and 318 patients with type 2 diabetes (T2DM) on long-acting BI for 6-36 months (BI users: current n=243 [self-titrating n=95], discontinued n=75), evaluated drivers of and barriers to optimal BI titration in the U.S., France and Germany. HCPs preferred higher fasting SMPG targets than guidelines recommend (Table). For current BI users, mean start dose was 15 U and mean current dose was 25 U. A dose increase of <10 U was seen by 27 months for 62% of current BI users despite 49% of them reporting not reaching HbA_{1c} target. Main barriers to optimal titration for current BI users not reaching HbA_{1c} target were concerns over weight gain (52%), frustration over time to reach goal (43%) or perception that dose increase meant worsening of disease (38%) (Table). HCPs perceived the main barriers to target attainment in self-titrating patients to be fear of hypoglycemia (74%) and low patient involvement/motivation (63%) (Table). The percentage of current BI users preferring self-titration (26%) was lower than current BI users self-titrating (39%). In conclusion, HCPs prefer a slow and safe approach to titration to avoid hypoglycemia, but patients not at target are frustrated about time taken to reach target and are less concerned about hypoglycemia than HCPs. Preference for self-titration needs improving and patients need encouraging to self-titrate.

Table. Survey Results.

HCP responses		Overall	USA			France		Germany	
HCP specialty		Overall (N=347)	PCP (N=104)	NP (N=27)	CDE (N=25)	Endo / Diabeto (N=67)	Nurse / CDE (N=27)	PCP (N=68)	Endo / Diabeto (N=29)
Mean recommended fasting SMPG target (mg/dL)	General	N/A	135	124	N/A	111	N/A	145	142
	Elderly	N/A	141	130	N/A	135	N/A	153	159

Responses for current BI users not at HbA_{1c} target and HCPs		Overall		USA		France		Germany	
		Patients (N=118)	HCPs (N=376)	Patients (N=59)	HCPs (N=171)	Patients (N=30)	HCPs (N=104)	Patients (N=29)	HCPs (N=101)
Barriers to titration for patients, and HCPs' perception of patients' barriers to reaching target in patients who self-titrate (%)[a]	Concern about weight gain	52	57	49	50	63	71	45	55
	Frustration that time to reach goal is too long	43	52	37	63	57	38	41	49
	Dose increase means disease is getting worse	38	55	31	58	53	70	38	34
	Fear of hypoglycemia	37	74	27	67	63	87	31	74
	Low motivation and involvement	27	63	22	65	33	56	31	67

[a]Multiple answers could be selected. BI, basal insulin; CDE, certified diabetes educator; Diabeto, diabetologist; Endo, endocrinologist; HCP, healthcare professional; N/A, not applicable; NP, nurse practitioner; PCP, primary care physician; SMPG, self-monitored plasma glucose.

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973-P

The Impact of Baseline Lung Function on Outcomes with Inhaled Technosphere Insulin (TI)

JOSEPH BRAIN, NIKHIL AMIN, JOHN STEWART, ELENA NIKONOVA, ROBERT WISE, *Boston, MA, Danbury, CT, Laval, QC, Canada, Morristown, NJ, Baltimore, MD*

TI is a novel inhaled rapid-acting insulin (RAI) approved for use in the U.S. This analysis explored the impact of baseline lung function on clinical outcomes and lung function changes in patients with T1D or T2D initiating inhaled TI therapy.

This pooled analyses of 7 studies (duration 6-24 months) included 949 patients with T1D and 1,132 with T2D using TI. Patients were stratified based on baseline percent predicted forced expiratory volume in 1 second (FEV_1PP): 70% to <80%, 80% to <90%, 90% to < 100%, and ≥ 100%. Differences among strata were assessed with one-way ANOVA analysis for demographics and regression modeling (MMRM) for FEV_1 change.

Patients in the lowest strata were older, and more had T2D than in the higher strata; they also had the lowest baseline FEV_1 for T1D. Baseline FEV_1 did not differ across strata for T2D (Table). There were no significant differences among the baseline FEV_1PP groups for the proportion of patients experiencing hypoglycemia, reporting cough, or reaching A1c < 7.0%, or in A1c at the end of the study (Table). The decline in lung function from baseline to 3 months was small and not significantly different among the groups.

The results show that patients with lower baseline lung function (70-80% of predicted normal at baseline) experienced similar glycemic efficacy, hypoglycemia, and lung function changes after 3 months when compared to those with better baseline lung function.

Table. Clinical Outcomes and Lung Function Changes in Patients Stratified by Baseline FEV_1PP.

	FEV_1PP				*P* Value
	70 to < 80% (n = 145)	80 to < 90% (n = 456)	90 to < 100% (n = 696)	≥ 100% (n = 784)	
Age, years (SD)	51 (13)	48 (13)	46 (14)	49 (14)	< 0.0001
Female, n (%)	60 (41.4)	196 (43.0)	332 (47.7)	384 (49.0)	0.1071
Diabetes type					
T1D	54 (37.2)	206 (45.2)	350 (50.3)	339 (43.2)	0.0073
T2D	91 (62.8)	250 (54.8)	346 (49.7)	445 (56.8)	
End of Study A1c < 7.0%, n (%)	14 (10.8)	64 (15.2)	97 (15.1)	121 (17.0)	0.3228
End of Study A1c, % (SD)	8.30 (1.20)	8.20 (1.30)	8.15 (1.35)	8.06 (1.25)	0.1410
Adverse event, n (%)	112 (77.2)	386 (84.6)	563 (80.9)	601 (76.7)	0.0057
Hypoglycemia, n (%)	51 (35.2)	184 (40.4)	284 (40.8)	302 (38.5)	0.5554
Reporting cough, n (%)	38 (26.2)	137 (30.0)	221 (31.8)	219 (27.9)	0.3291
Baseline FEV_1, L (SE)					
T1D	2.73 (0.54)	3.11 (0.62)	3.44 (0.63)	3.83 (0.82)	< 0.0001
T2D	2.99 (0.68)	2.47 (0.48)	2.79 (0.55)	2.98 (0.62)	< 0.0001
FEV_1 change from baseline to 3 months, LS mean, L (SE)					
T1D	–0.023 (0.22)	–0037 (0.020)	–0.048 (0.009)	–0.043 (0.009)	0.7785
T2D	–0.059 (0.020)	–0.056 (0.012)	–0.078 (0.009)	–0.055 (0.010)	0.2243

P values in the Table come from a one-way ANOVA analysis, except for the change in FEV_1 from baseline to 3 months, which was analyzed by mixed effect model repeated measurement (MMRM) in baseline FEV_1; age, gender, and height were included as covariates. LS means, least square means.

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974-P

Looking for Predictors of Successful Basal Insulin Titration in T2DM

MICHEL P. HERMANS, SYLVIE A. AHN, MICHEL F. ROUSSEAU, *Brussels, Belgium*

Adjusting insulin dose after initiation is a key component of regimens combining basal insulin with oral therapies. Most T2DM patients titrate an initial dose of basal insulin administered in the evening/ bedtime according to incremental algorithms for target glucose, while minimizing hypoglycemia. Disappointingly, most patients do not reach glycemic target, due to untimely/ unjustified arrest during titration, even in the absence of hypoglycemia.

We studied the characteristics distinguishing patients able ("good titrators" [GT]) or unable ("poor titrators" [PT]) to reach target pre-meal morning glucose <130 mg/dL following initiation of basal insulin (bedtime NPH/ glargine; initial dose: 2 U; titration: +2U/72 h) in 112 T2DM (81% white Caucasians) in secondary failure to oral glucose-lowering drugs.

[GT] amounted to 41% (n=46). They did not differ from [PT] (n=66; 59%) in terms of age; ethnicity; gender; diabetes duration (total/prior to insulin); β-cell function and loss rate; pre-insulin HbA1c; metabolic syndrome; Metformin dose; basal insulin dose (38 vs. 36 U/day in [PT]); capillary glucose measurement frequency; renal function; CV drugs; vascular complications; and lipids/lipoproteins.

A normal BMI was present in 43% of [GT] vs. 24% of [PT] (p 0.0404). HbA1c was 7.45% in [GT] vs. 8.62% in [PT] (p<0.0001). Pre-meal morning glucose was 112 mg/dL in [GT] vs. 168 mg/dL in [PT]. Socio-education level (lower/ higher (%)) was greater in [GT]: 33/67% vs. 55/45% in [PT] (p 0.0334). Insulin sensitivity was higher in [GT]: 58% vs. 38% in [PT] (p 0.0015). Benzodiazepines use was 33% in [GT] vs. 15% in [PT] (p 0.0382). Frequency of low (<70 mg/dL) glucose or severe hypoglycaemia was 6%-1.4%/yr [GT] vs. 1%-0.2%/ yr [PT] (p 0.0031 and <0.0001).

In T2DM patients, this analysis identified 4 variables associated with successful patient-driven titration of physician-initiated basal insulin supplementation, namely higher socio-educational level, having a normal BMI; greater insulin sensitivity, and benzodiazepines use.

975-P

A Population PK/PD Model of Technosphere® Insulin Administered to Healthy Subjects

DIETHER RUEPPEL, RAPHAEL DAHMEN, ANDERS BOSS, MARSHALL GRANT, ROBERT BAUGHMAN, THOMAS KLABUNDE, *Frankfurt, Germany, Bridgewater, NJ, Danbury, CT*

A large percentage of patients with type 2 diabetes are treated with multiple daily insulin injections. Technosphere® insulin (TI), an inhaled insulin with a fast onset of action, provides a novel option for the control of prandial glucose. The aim of this analysis is to a) quantify the dose response relation-

For author disclosure information, see page A696.

ship for TI in comparison to subcutaneously (sc) administered regular human insulin (RHI) and b) compare the onset and duration of action of TI and RHI.

Population PK and PK/PD models were developed using data from an euglycemic glucose clamp study in 32 healthy volunteers, each receiving one dose of sc regular human insulin (15 IU) and 4 doses of TI (10 TI U, 30 TI U, 60 TI U, 80 TI U). The glucose infusion rate (GIR) was recorded for 4 hr following each dose of TI and 10 hr following administration of RHI. The population PK/PD model (PK-GIR model) was based on an E_{max} model to relate insulin concentrations from an effect compartment to the glucose infusion rate (GIR). In a second step, a dose response model was developed relating insulin doses of TI and RHI with the area under the curve (AUC) of GIR, also by an E_{max} model (dose-GIR_{AUC} model). GIR AUCs were calculated until 20 hr to ensure that GIR values have returned to baseline to capture the full PD effect. GIR values beyond the last observation were simulated from the PK-GIR model. GIR time curves for doses of TI or RHI not measured in the study, but necessary to capture the dose-response relationship, were also calculated from the PK-GIR model. The dose-GIR_{AUC} model suggests that the dose-response for TI and RHI can be described by a linear relationship for therapeutically relevant doses (RHI up to 16 IU and TI up to 80 TI U).

Finally, GIR time curves were simulated for a RHI dose of 8 IU and a TI dose of 40 TI U, i.e., a dose providing an equivalent PD effect (as expressed by GIR-AUC). The onset of action was found to be faster for TI as expressed by steeper cumulative GIR_{AUC} curves and shorter times to reach the half maximal effect (RHI, 296±64 min vs. TI, 124±25 min). (NCT01490762).

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976-P

Combination Use of Liraglutide and Insulin to Subjects under Reasonable Glycemic Control with Multiple Insulin Injection

MASAFUMI MATSUDA, YOSHITAKA AKIYAMA, TOMOKO MORITA, HOUDA SELLAMI-MNIF, HIROYUKI OTAKE, YOSHIMI ABE, REIE MATOBA, ANNA SAKASHITA, SHINYA MINAGAWA, SEIKI WADA, MASAKO YAZAWA, EIJI OMURA, *Kawagoe, Japan*

Efficacy and safety of the combination use of a GLP-1 receptor agonist and basal insulin has been well established. However, in the real world, switching from multiple insulin injection to this combination in patients who already have a reasonable glycemic control has not been well documented. Since the switching from multiple insulin injection usually reduces the frequency of injection, the quality of life should be improved. We compared groups, one with a reasonable control (RC: HbA1c < 8%) and another with a poor control (PC: HbA1c > =8%). Among 92 type 2 diabetic patients (age: 59±13 y.o., M/F: 45/47, BMI: 28±5 kg/m^2, HbA1c: 8.3±1.8%, duration of diabetes 12.9±8.2 years, C-peptide index: 2.6±1.5) who started the simultaneous injection of liraglutide and insulin in the morning, 45 subjects were classified into PC while 47 subjects were into RC. Except for HbA1c, there were no statistical differences between RC and PC. All the subjects continued the combination treatment for an observational period for 272±101 days. Bolus insulin was 14±9 units before the combination therapy. The doses of basal insulin were adjusted to achieve the fasting PG of 90-120mg/dl. Average daily dose of liraglutide was 0.86±0.14 mg, while basal insulin was increased from 17±14 to 20±13 units. HbA1c was significantly improved from 9.6±1.6 and 7.0±0.6 to 8.0±1.5 and 6.8±0.5% in PC and RC respectively. Reduction of body weight was significant only in RC (from 70±16 to 68±16 kg, $p < 0.01$ vs. before). In PC body weight was changed from 73±14 to 75±16 kg. 100% of RC and 58% of PC reached HbA1c < 8%. No severe hypoglycemia was reported. This observation persuades us to introduce patients who are even already under reasonable glycemic control with multiple insulin injection to the combination of a GLP-1 receptor agonist and basal insulin.

977-P

Ultrasonographic Detection of Lipohypertrophy: Criteria and Comparison of Standard Clinical Examination

JORDANNA KAPELUTO, BREAY W. PATY, SILVIA D. CHANG, GRAYDON MENEILLY, *Vancouver, BC, Canada*

Lipohypertrophy (LH) is a prevalent complication of insulin therapy that has been demonstrated through the use of ultrasonography (US), however no standard criteria for its detection have been proposed. The objectives of the study were to characterize LH using US and compare detection to clinical examination (CE). Ultrasound criteria for LH were determined by characterizing LH in patients (n=7) identified as having LH on physical examination. Image analysis demonstrated an echo signature consisting of the presence of heterogeneous or hyperdense echogenicity, a well-circumscribed area and connective tissue distortion in the absence of vascularity or capsule. A random cohort of 51 patients on insulin therapy (n=6 T1DM, n=45 T2DM) underwent CE followed by US performed by a single, blinded operator. Palpable LH was found in 67% of patients (n=34). Sixty-two areas identified as LH were found on CE and 105 areas meeting US criteria were noted with moderate intra observer correlation between modalities (κ= 0.41). LH was detected by US significantly more frequently than CE ($p<0.001$). Sixty-six areas ($P<0.001$) meeting US criteria did not correlate with palpable LH on CE and may represent subclinical LH. These subclinical findings were found in 22% of patients (n=11) without palpable LH, and 61% (n=31) had both subclinical findings and palpable LH. Additionally, six areas of LH identified on CE were consistent with lipoma or cyst when assessed by US. Our findings provide criteria for the detection of LH using ultrasonography with correlation to standard clinical examination. Furthermore, these results suggest a role for ultrasonography in detecting early changes to the subcutaneous tissue and that cysts and lipomas may be misidentified as LH on clinical examination.

978-P

Comparative Effectiveness of Various Long-Acting (Lantus, Levemir), Rapid-Acting (Apidra, Humalog, Novalog) Insulin Analogs and Their Combinations for Type 1 Diabetes (T1D) Patients

ALYSSA WOODWYK, CRAIG BEAM, *Kalamazoo, MI*

The goal of this study was to compare the effectiveness of long acting (Lantus, Levemir), rapid acting (Apidra, Humalog, Novalog) insulin analogs and their combinations using clinical outcomes data from the T1D Exchange (https://t1dexchange.org/pages/). From the 25,762 subjects available, we selected 1,245 adults (19+) who had hyperglycemia (HbA1c>6.5 mmol/mol) with a subsequent follow-up visit within 6 months. In our study, 54.38% were female, 56.14% were 19-40 years old, 96.06% were treated with rapid acting insulin, 34.06% were treated with long acting insulin, and 33.09% were treated with both. Mean (SD) age was 38.98 (17.2) years; initial HbA1c 8.05 (1.34) mmol/mol; follow-up HbA1c 7.95 (1.32) mmol/mol; and HbA1c change -0.10 (1.02) mmol/mol. After statistically controlling for age group, gender and BMI group with ANOCOVA, significant reductions in HbA1c (mean: 95% CI) were found in subjects treated solely with Lantus (-0.85:-1.42, -0.29), Humalog (-0.13:-0.23, -0.03) and Novolog (-0.15: -0.24, -0.06). Only the combination of Novolog and Levemir was found to be effective in reducing HbA1c (-0.56:-0.99, -0.12). In effectiveness comparisons, solo therapy with Lantus was found to be significantly ($p<0.05$) more effective than Humalog ($p=0.013$), Aprida ($p=0.002$) and Novalog ($p=0.016$) solo therapies. No other comparisons of solo therapies were significant. The combination of Humalog and Levemir was significantly more effective than solo therapies with either Novolog ($p=0.049$) or Lantus ($p=0.002$). Subsequent "responder analysis" using multiple logistic regression found that Lantus increased the odds of response (reduction in HbA1c from abnormal to normal range): OR=6.909: 95% CI (2.15, 22.17). Our findings therefore agree with the conclusions recently reached by Tricco et al (BMJ 2014;349:g5459) that long acting analogs are superior to intermediate acting insulin analogs.

979-P

Impact of Switching to Insulin Degludec in Japanese Patients with Diabetes under Multiple Insulin Injections

TOSHIHIKO OHAMA, KOZO KATSUMORI, AI SATO, TOSHIHIKO SAITO, SATOSHI TANAKA, MARIKO SUETSUGU, MIHO OKAWARA, OSAMU TOMONAGA, TOMOKO NAKAGAMI, *Saitama, Japan, Tokyo, Japan*

Aim: There have been few reports regarding the change in insulin dose over time after switching to insulin Degludec (IDeg). We examined the impact of switching of basal insulin from neutral protamine hagedorn (N), insulin detemir (D), or insulin glargine (G) to IDeg in Japanese patients with diabetes (DM) under multiple insulin injections.

Methods: A total of 74 patients with DM who had been treated by other types of insulin were followed up for 52 weeks after switching to IDeg. The patients were classified according to baseline insulin into three groups: G (n=43), D (n=18), and N (n=13), and group G was further classified by type of diabetes into G1 (type 1 DM, n=23) and G2 (type 2 DM, n=20). The dose of IDeg was adjusted to achieve the fasting plasma glucose of <130 mg/dL. The linear regression model was used to analyze the effects of clinical characteristics on 52 weeks change in HbA1c or basal insulin dose (BID) in the above-mentioned groups separately.

Results: HbA1c improved from 8.9%±1.5 to 8.2%±1.4% by switching to IDeg in 74 patients ($P<0.01$). The BID at weeks 0 and 52 after switching to IDeg in patients with G1, G2, D, and N were 14.0±8.1 and 16.1±9.0 IU ($p=0.02$), 11.2±4.3 and 11.5±4.5 IU ($p=0.22$), 9.4±4.1 and 9.1±3.9 IU ($p=0.85$), and 11.2±4.6 and 9.6±3.1 IU ($p=0.07$), respectively. The change in HbA1c was negatively related to HbA1c at baseline in patients with G1 ($p=0.02$), D ($P<0.01$), and N ($P<0.01$) while positively related to duration of DM in those with G2 ($P<0.01$). The change in BID was negatively related to BID at baseline in patients with G2 ($P=0.04$), D

(P=0.04), and N (P<0.01) while positively related to body weight at baseline in those with D (P<0.01). The BID where BID did not change by switching to IDeg in the patients with G2, D, and N were 14, 7 and 8 IU respectively.

Conclusion: The change in BID after switching to IDeg was significantly and negatively related to BID at baseline, and BID was expected to be reduced if the baseline BID was 14 IU (0.23 IU/kg) or higher in our Japanese patients with DM.

980-P

Clinical Outcomes in Asian and Non-Asian People with Type 2 Diabetes (T2D) Initiating Glargine 100 Units/mL (Gla-100) Therapy: Results of a Pooled Analysis from 16 RCTs

JULIANA C.N. CHAN, PONGAMORN BUNNAG, SIEW PHENG CHAN, IRIS THIELE ISIP TAN, SHIH-TZER TSAI, LING GAO, WOLFGANG LANDGRAF, *Hong Kong, China, Bangkok, Thailand, Kuala Lumpur, Malaysia, Manila, Philippines, Taipei, Taiwan, Somerset, NJ, Frankfurt, Germany*

T2D is an epidemic disease in Asia, with younger age and lower BMI at diagnosis in Asians vs. non-Asians.

This subject-level analysis compared outcomes in Asians and non-Asians with T2D from 16 RCTs (target FPG ≤ 100 mg/dL, ≥ 24-week duration) adding Gla-100 to OADs. Data from Asians and non-Asians were compared overall and by concomitant OAD therapy at baseline and week 24.

Of 3,586 participants, 235 were Asian. The majority (n = 111) received Gla-100 and Metformin (MET) plus sulfonylurea (SU). Outcomes at week 24 for overall and MET + SU groups are shown in the Table. Overall, Asians were younger, had lower BMI, but similar baseline (BL) HbA1c vs. non-Asians. Final insulin doses (0.44 U/kg) were similar in both groups with greater HbA1c reductions and HbA1c ≤ 7.0% achievement in non-Asians. Asians had lower BL FPG with a tendency towards greater FPG reductions ($P > 0.05$) but higher HbA1c at endpoint than non-Asians, suggesting poorer β-cell function. In those treated with MET + SU, Asians had higher endpoint HbA1c at lower Gla-100 dose vs. non-Asians. Hypoglycemia and weight gain were lower in Asians than non-Asians.

At similar Gla-100 doses and hypoglycemia incidence, the proportion of Asians with T2D at HbA1c target is smaller than in non-Asians, suggesting higher daily insulin doses or additional antidiabetes drugs are needed for adequate glycemic control.

Table. Clinical Outcomes in Asian and Non-Asian People with T2D Initiating Gla-100 Therapy.

	Gla-100 Overall			Gla-100 + MET + SU		
Parameter (SD)	**Asian (n=235)**	**Non-Asian (n=3,351)**	***P* Value**	**Asian (n=111)**	**Non-Asian (n=1,513)**	***P* Value**
Baseline						
Age, years	53.7 (9.0)	57.9 (9.7)	< 0.001	54.1 (8.8)	58.5 (9.1)	< 0.001
Diabetes duration, years	8.9 (6.0)	8.9 (6.2)	0.92	9.6 (4.8)	9.4 (6.3)	0.74
Weight, kg	70.4 (12.6)	87.3 (18.1)	< 0.001	70.1 (13.2)	88.6 (17.0)	< 0.001
BMI, kg/m^2	27.1 (3.9)	30.8 (5.3)	< 0.001	27.3 (4.3)	31.2 (4.9)	< 0.001
HbA1c, %	8.6 (1.0)	8.7 (1.1)	0.08	8.4 (0.9)	8.6 (1.0)	0.04
FPG, mg/dL	169 (46)	194 (55)	< 0.001	160 (38)	189 (52)	< 0.001
Insulin dose, U/kg	0.18 (0.04)	0.16 (0.08)	< 0.001	0.17 (0.04)	0.14 (0.05)	< 0.001
Week 24 endpoint						
Adjusted HbA1c, %	7.42 (0.06)	7.16 (0.02)	< 0.001	7.16 (0.08)	7.07 (0.02)	0.27
Adjusted HbA1c change from baseline	–1.30 (0.06)	–1.55 (0.02)	< 0.001	–1.41 (0.08)	–1.50 (0.02)	0.27
HbA1c ≤ 7.0 %, n (%)	90 (41.9)	1605 (50.7)	< 0.001	44 (43.1)	783 (53.8)	0.14
Adjusted FPG change from baseline, mg/dL	–78.1 (2.6)	–75.2 (0.7)	0.27	–74.4 (3.7)	–68.3 (0.9)	0.11
FPG ≤ 100 mg/dL, n (%)	101 (47.6)	1076 (34.0)	0.21	44 (44.9)	468 (32.5)	0.37
Adjusted hypoglycemia[a], events per patient-year	4.3 (0.6)	5.5 (0.2)	0.09	6.5 (1.1)	7.4 (0.3)	0.45
Adjusted weight change from baseline, kg	1.3 (0.2)	1.9 (0.1)	0.01	1.4 (0.3)	1.8 (0.1)	0.25
Adjusted insulin dose, U/kg	0.47 (0.02)	0.45 (0.00)	0.16	0.36 (0.02)	0.41 (0.01)	0.045

Data presented represent mean (SD) for baseline and adjusted mean (SE) for week 24 endpoint, except for items n (%). [a]Overall hypoglycemia defined as PG < 70 mg/dL or third-party assistance required. FPG, fasting plasma glucose; SD, standard deviation; SE, standard error.

Supported By: Sanofi

981-P

Efficacy of Lixisenatide Compared with Prandial Insulin by Patient Characteristics

HELENA W. RODBARD, VANITA ARODA, TERRY DEX, ELENA NIKONOVA, YAN YAN, TIMOTHY S. BAILEY, *Rockville, MD, Hyattsville, MD, Bridgewater, NJ, Morristown, NJ, King of Prussia, PA, Escondido, CA*

We investigated whether there are patient characteristics that may help guide the selection of therapy for treatment intensification in patients with T2D who have not reached target A1c using basal insulin (BI).

In the GetGoal Duo 2 trial, patients with T2D inadequately controlled with BI had treatment intensified with the glucagon-like peptide-1 receptor agonist lixisenatide QD (LIXI; in development in the U.S.), or with insulin glulisine QD (GLU-QD) or TID (GLU-TID): at baseline mean age was 60, 60, and 59 y; 46, 45, and 44% were male; mean BMI was 32, 32, and 33 kg/m^2; mean A1c was 7.8, 7.7, and 7.8%; mean diabetes duration was 12 y for all. Achievement of A1c < 7.0% and the composite endpoint (A1c < 7.0% with no hypoglycemia [plasma glucose < 60 mg/dL] and no weight gain) were assessed in a post-hoc analysis.

LIXI use led to comparable achievement of A1c < 7.0% and significantly greater achievement of the composite endpoint compared to GLU-QD and -TID across multiple patient demographic categories (Table). Within treatment groups, patient characteristics did not affect likelihood of achieving primary and composite outcomes, with the exception of baseline A1c and BMI (Table).

These results suggest that the choice of therapy for intensification of treatment does not need to be guided by the patient's baseline characteristics, and when trying to achieve the composite endpoint LIXI is superior to GLU-QD or -TID.

Table. Endpoint (Week 24) Achievement of Composite Endpoint[a] by Baseline Characteristics.

Baseline Characteristic	**LIXI (n=298)**	**GLU-QD (n=298)**	**LIXI vs. GLU-QD *P* Value[b]**	**GLU-TID (n=298)**	**LIXI vs. GLU-TID *P* Value[b]**
A1c					
< 8.0% (n/N)	25.6% (50/195)	9.9% (19/191)	**< 0.001**	15.1% (28/185)	**0.011**
≥ 8.0% (n/N)	15.7% (16/102)	7.8% (8/103)	0.078	3.6% (4/110)	**0.003**
P value[b]	0.050	0.537		**0.002**	
Age					
< 65 years (n/N)	21.6% (45/208)	10.4% (21/202)	**0.002**	11.9% (24/201)	**0.009**
≥ 65 years (n/N)	23.6% (21/89)	6.5% (6/92)	**0.001**	8.5% (8/94)	**0.005**
P value[b]	0.710	0.286		0.377	
BMI					
< 30 (n/N)	14.4% (14/97)	12.1% (14/116)	0.611	4.1% (4/97)	**0.013**
30-35 (n/N)	26.3% (31/118)	7.6% (8/105)	**< 0.001**	10.9% (11/101)	**0.004**
≥ 35 (n/N)	25.6% (21/82)	6.8% (5/73)	**0.002**	17.5% (17/97)	0.188
P value[b]	0.079	0.379		**0.011**	
Gender					
Male (n/N)	18.1% (25/138)	11.3% (15/133)	0.113	13.1% (17/130)	0.257
Female (n/N)	25.8% (41/159)	7.5% (12/161)	**< 0.001**	9.1% (15/165)	**< 0.001**
P value[b]	0.113	0.258		0.274	
Duration of diabetes					
< 10 years (n/N)	27.5% (33/120)	11.0% (13/118)	**0.001**	12.4% (16/129)	**0.003**
≥ 10 years (n/N)	18.6% (33/177)	8.0% (14/176)	**0.003**	9.6% (16/166)	**0.017**
P value[b]	0.072	0.373		0.449	

[a]Composite endpoint: A1c < 7.0% with no hypoglycemia (plasma glucose < 60 mg/dL) and no weight gain. [b]Analyzed by Pearson Chi-square test. Bold denotes $P < 0.05$.

Supported By: Sanofi U.S.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

Moderated Poster Discussion: Improving the Safety of Insulin Management with Technology and Smart Systems *(Posters: 982-P to 989-P), see page 14.*

982-P

Insulin Pharmacodynamics and Outcomes during Home Use of Closed-Loop Insulin Delivery in Adults with Type 1 Diabetes

YUE RUAN, HOOD THABIT, LALANTHA LEELARATHNA, SARA HARTNELL, MALGORZATA E. WILINSKA, SIBYLLE DELLWEG, CARSTEN BENESCH, JULIA K. MADER, MANUEL HOLZER, HARALD KOJZAR, MARK L. EVANS, SABINE ARNOLDS, THOMAS PIEBER, ROMAN HOVORKA, *Cambridge, United Kingdom, Manchester, United Kingdom, Neuss, Germany, Graz, Austria*

The relationship between insulin pharmacodynamics and performance of closed-loop insulin delivery is not fully understood. We retrospectively analysed data collected during a multicentre multinational study of free-living 12-week home use of day-and-night hybrid closed-loop insulin delivery involving 32 adults with type 1 diabetes [male/female 17/15, age 40 (10) years, BMI 25.4 (4.4) kg/m^2, HbA1c at start of closed loop 60 (7) mmol/mol; mean (SD)]. Hierarchical Bayesian compartment modelling of 2569 days of closed-loop use provided estimate of each participant's time-to-peak of insulin action [$t_{max,\ IA}$; 79 (12) min] and insulin sensitivity 0.0047 (0.0012) mmol/l per mU/l] from sensor glucose data, insulin delivery, and carbohydrate content of meals. $t_{max,\ IA}$ was positively correlated with BMI, pre- and post-study HbA1c, and glucose variability (CV of sensor glucose) whilst being inversely correlated with time sensor glucose was in target range during closed loop (Table). Insulin sensitivity was negatively correlated to BMI but not to glucose control. In conclusion, delayed time to peak of insulin action but not impaired insulin sensitivity hinders performance of closed-loop insulin delivery. Accelerating insulin action is priority for closed-loop research.

Table. Spearman's Rank Correlation (N=32), * $p < 0.05$; ** $p < 0.01$.

	Age	BMI	HbA1c pre closed loop	HbA1c post closed loop	Time in target	Time <3.9mM	Glucose variability
Time-to-peak of insulin action	-0.02	**0.38***	**0.37***	**0.42***	**-0.56****	-0.12	**0.43***
Insulin sensitivity	0.19	**-0.38***	0.08	-0.11	-0.10	-0.07	0.03

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983-P

In Silico Testing of an Artificial Intelligence-based Artificial Pancreas Designed for Use in the Intensive Care Unit Setting

LEON DEJOURNETT, JEREMY DEJOURNETT, *Asheville, NC*

Effective glucose control in the Intensive Care Unit (ICU) setting has the potential to save thousands of lives and billions of dollars in healthcare resources annually. Current ICU glucose controllers are mathematically derived, and are either proportional integral derivative (PID) or model predictive control (MPC) based. Artificial Intelligence (AI) based glucose controllers have the ability to achieve control that improves upon the results achieved by PID or MPC controllers.

We conducted an in silico analysis of an AI based glucose controller designed for use in the ICU setting. This controller was tested using a mathematical model of the ICU patient's glucose-insulin system. A total of 126,000 unique 5 day simulations were carried out, resulting in 107 million glucose values for analysis.

The Mathematical model used was originally developed by Van Herpe and was modified for this study as noted below:

$dG(t)/dt = (P_1 - i_s(t)X(t))\ G(t) - P_1G_b + (F_{CG} + F_{EG}/V(t)V_G)$, (1); $dX(t)/dt = P_2X(t) + P_3\ (I_2(t) - I_b)$, (2); $dI_1(t)/dt = \alpha$ max $(0, I_2) - n\ i_h(t)\ (I_1(t) - I_b) + (F_{CI}/V(t)V_I)$, (3); $dI_2(t)/dt = \beta\gamma\ (G(t) - h) - n\ i_h(t)I_2(t)$, (4); $i_s(t)$, $V(t)$ and $i_h(t)$ are time variant multipliers of insulin sensitivity, volume of distribution and insulin half life. F_{CG} is the dextrose flow from the controller and F_{EG} is the exogenous dextrose flow used to perturb the system. F_{CI} is the insulin flow from the controller.

For the seven control ranges tested, with a sensor error of ±10%, the following average results were achieved: 1.) time in control range 93.4%, 2.) time in range 70-140 mg/dl 97.3%, 3.) time in hyperglycemic range (>140 mg/dl) < 2.6%, and 4.) time in hypoglycemic range (<70 mg/dl) < 0.1%. In addition, the average coefficient of variation (CV) was < 11%.

This in silico study of an AI based glucose controller shows its potential superior performance vs. current PID/MPC controllers. If confirmed in clinical testing, this AI based controller could be used to create an artificial pancreas system.

984-P

Impact of Endocrine Care on Glycemic Management in Type 2 Diabetes (T2DM) Using either Continuous Subcutaneous Insulin Infusion (CSII) or Multiple Daily Insulin Injections (MDI)

POOJA MANROA, LAURA POTOSKI, EMILY MARTIN, R. HARSHA RAO, *Pittsburgh, PA*

The indications and benefits of CSII in T2DM remain uncertain because previous studies have shown mixed results. A recent multicenter randomized controlled trial (OpT2mise) showed a short-term (6 month) glycemic benefit from CSII in patients with persistent poor control after optimization of MDI, but it is unknown if the benefit persists. The objective of this retrospective study was to compare glycemic control in T2DM managed with either MDI (n=273) or CSII (n=70) by a group of endocrinologists adhering to a uniform policy for both. Demonstrated proficiency in essential pump related skills like carbohydrate counting was a prerequisite for CSII therapy. We assessed magnitude and sustainability of glycemic benefit using average A1c before and during endocrine care over prolonged follow-up (Mean±SE, MDI 3.0±0.1 y, CSII 6.0±0.5, p<0.001). Average A1c was higher before starting MDI (9±0.1 vs. CSII 8±0.2%, p<0.001), therefore A1c decline was greater (0.6±0.1 vs. CSII 0.3±0.1, p=0.02); however, sustained A1c with CSII was lower (7.7±0.1 vs. MDI 8.4±0.1, p<0.001). In patients with poor control (prior A1c ≥7.9), the A1c decline was similar (MDI 0.9±0.1 vs. CSII 0.8±0.2, p=0.8), but sustained A1c on CSII was lower in this subset as well (8.1±0.1 vs. MDI 8.6±0.1, p=0.001). In the CSII group with poor control, sustained A1c improvement occurred both in patients who came to endocrine care on prior CSII (0.9±0.3, p=0.002), and in those transitioned to CSII from MDI (0.7±0.2, p<0.001). In patients switched to CSII for hypoglycemia, A1c remained unchanged at 7.1 (p=0.9) despite eliminating hypoglycemia. We conclude that CSII in T2DM achieves and maintains lower A1c compared to MDI by the same endocrinologists, as long as patient selection is restricted to those with skills requisite for CSII therapy. The benefit is sustained over 6 y of follow-up and is greatest in patients transitioned to CSII for A1c≥7.9 or recurrent hypoglycemia.

985-P

Glucose Concentrations and Rates of Change during Hypoglycemia Induction to Evaluate a Predictive Low Glucose Management (PLGM) System

SATISH GARG, MARK CHRISTIANSEN, RON BRAZG, TIMOTHY S. BAILEY, BRUCE BUCKINGHAM, STACEY M. ANDERSON, STUART WEINZIMER, BRUCE BODE, JOHN B. WELSH, FRANCINE R. KAUFMAN, *Denver, CO, Walnut Creek, CA, Renton, WA, Escondido, CA, Stanford, CA, Charlottesville, VA, New Haven, CT, Atlanta, GA, Northridge, CA*

Predictive algorithms based on continuous glucose monitoring data are the basis for automatic suspension and resumption of insulin delivery by the PLGM feature of the MiniMed 640G insulin pump system. The suspend before low and auto-resume features use a combination of existing and predicted sensor glucose (SG) values. Activation of the suspend before low feature triggers a 30-min refractory period during which the auto-resume feature is disabled. This study evaluated the performance of the system in experiments in which basal insulin delivery was increased per a protocol to induce hypoglycemia in subjects ages 14-74 years with type 1 diabetes (T1D). Of the 69 experiments, the suspend before low and auto-resume features were activated in 68. Plasma glucose rates of change (ROCs) were calculated from the two values closest to each time point. The Table shows glucose values and ROCs at various times with respect to suspension and resumption of insulin delivery. Four hours after automated resumption of insulin delivery, the mean ±SD YSI glucose concentration was 151.6±38.24 mg/dL and ROC was 0.0±0.27 mg/dL × min^{-1}, indicating stabilization. The predictive algorithms for automatically suspending and resuming insulin delivery in the MiniMed 640G system are safe and effective in preventing hypo- and hyperglycemia in subjects with T1D.

Table. Glucose Concentrations and Rates of Change (ROC) with Respect to Insulin Suspension and Resumption.

	Time vs. Insulin Suspension		Time vs. Insulin Resumption	
Time (min)	Glucose (mg/dL)	ROC (mg/dL × min^{-1})	Glucose (mg/dL)	ROC (mg/dL × min^{-1})
-60	133.6±27.18	-0.4±0.47	83.7±23.48	-0.2±0.39
-30	119.8±23.61	-0.6±0.46	81.8±21.98	0.1±0.43
0	101.3±18.46	-0.6±0.56	93.5±23.43	0.6±0.8
+30	88.3±18.77	-0.2±0.48	113.4±35.40	0.6±0.68
+60	83.2±19.80	0.0±0.58	126.2±42.75	0.3±0.41
+120	101.6±34.56	0.5±0.73	139.1±45.92	0.2±0.54

Supported By: Medtronic

Clinical Diabetes/ Therapeutics POSTERS

986-P

Overnight Glucose Control with Dual- and Single-Hormone Artificial Pancreas in Type 1 Diabetes with Hypoglycemia Unawareness vs. Hypoglycemia Awareness: Randomized, Controlled Trial

ALEXANDER ABITBOL, RÉMI RABASA-LHORET, VIRGINIE MESSIER, LAURENT LEGAULT, MARTIN LADOUCEUR, AHMAD HAIDAR, *Oakville, ON, Canada, Montreal, QC, Canada*

The dual-hormone (insulin and glucagon) artificial pancreas may be justifiable in some but not all patients, among them are hypoglycemia unaware patients. We conducted a randomized crossover trial comparing dual- and single-hormone artificial pancreas over one night in 16 adult patients with hypoglycemia unawareness and 11 patients with hypoglycemia awareness. All patients had documented nocturnal hypoglycemia during two weeks of screening. Analysis was performed using plasma glucose. In patients with hypoglycemia unawareness, the time spent below 4 mmol/L was 0% [0-11] on single-hormone nights and 0% [0-0] on dual-hormone nights (P=0.29). In patients with hypoglycemia awareness, the time spent below 4 mmol/L was 0% [0-0] on single-hormone nights and 0% [0-4] on dual-hormone nights (P=0.78). In hypoglycemia unaware patients, there were 4 hypoglycemic events (< 3 mmol/L) on single-hormone nights and 2 events on dual-hormone nights. In hypoglycemia aware patients, there was 1 event on single-hormone nights and none on dual-hormone nights. None of the outcomes differed between the two patient groups. We conclude that the single-hormone artificial pancreas might be sufficient for hypoglycemia-free overnight control in patients with hypoglycemia unawareness. Day and night studies in this population are needed.

Table. Comparisons between Single- and Dual-Hormone Artificial Pancreas.

	Patients with hypoglycemia unawareness (N=16)			Patients with hypoglycemia awareness (N=11)		
Outcome	Single-hormone	P value	Dual-hormone	Single-hormone	P value	Dual-hormone
Time spent (%) between 4.0-8.0 mmol/L	66±32	0.98	65±32	58±21	0.07	74±19
Time spent (%) below 4.0 mmol/L	0 [0–11.1]	0.29	0 [0–0]	0 [0–0]	0.78	0 [0–11.1]
Time spent (%) below 3.5 mmol/L	0 [0–1.2]	0.27	0 [0–0]	0 [0–0]	0.94	0 [0–1.2]
Time spent (%) below 3.3 mmol/L	0 [0–0]	0.24	0 [0–0]	0 [0–0]	0.42	0 [0–0]
Mean glucose (mmol/L)	6.8±1.5	0.28	7.4±1.9	7.7±1.2	0.16	7.0±1.2
No. of hypoglycemia events	4	-	2	1	-	0

Supported By: JDRF

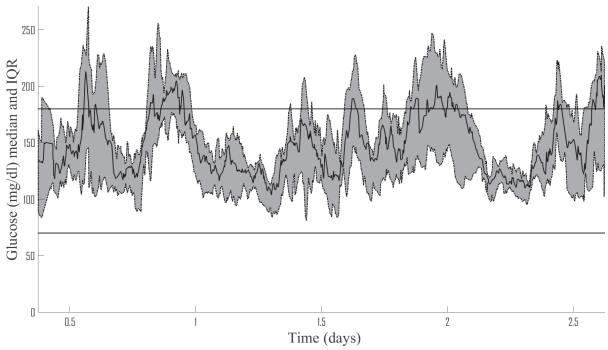
987-P

Hotel Trial of a Fully Closed-Loop Artificial Pancreas with Unannounced, Unscheduled Large Meals

FAYE CAMERON, NIHAT BAYSAL, BRUCE A. BUCKINGHAM, PAULA CLINTON, GREGORY P. FORLENZA, DANIEL HOWSMON, DAVID LAM, CAMILLA LEVISTER, CAROL LEVY, TRANG T. LY, DAVID M. MAAHS, LAUREL H. MESSER, STEPHEN D. PATEK, EMILY WESTFALL, YAN YAN XIE, B. WAYNE BEQUETTE, *Troy, NY, Stanford, CA, Denver, CO, New York, NY, Aurora, CO, Charlottesville, VA*

A fully closed loop artificial pancreas (AP) was tested at 3 hotels at 3 clinical sites on 15 subjects for a total of 31 days. The controller used an activity monitor, a CGM, as well as wake and sleep announcements. The patient's basal rates total daily dose were used to tune the controller. The AP was implemented on the UVA DiAs system with a Roche Spirit Combo Insulin Pump, a Dexcom G4 Continuous Glucose Monitor, and a Zephyr BioHarness 3.0 accelerometer. Therapy ran from 9 AM to roughly 3 PM two days later. Subjects ate when, what, and as much as they desired. Meals were neither announced nor bolused. Subjects had several periods of mild exercise such as walking and running. The 15 subjects (13 female) had a mean (range) age of 30 (14-51) yrs; daily insulin requirements of 0.7 (0.4-1.7) u/kg/day; and HbA1c of 7.0% (5.8-8.8). During the trial, average daily CHO's were 230 g (92-355). Hypoglycemia interventions averaged 19 g CHO/day. On a 24-hour basis, the mean CGM was 152 mg/dl, with 73% of time between 70 and 180 mg/dl, 1.5% < 70 mg/dl, 0.1% <50 mg/dl, and 5.9% above 250 mg/dl. Overnight (11 PM to 7 AM) 83% of CGM readings were within 70 and 180 mg/dl, with a mean of 141 mg/dl. There were no CHO interventions overnight. The controller maintained good control in a hotel setting against repeated unannounced meals of variable size and mild exercise. It should now be tested in an outpatient setting with more varied activity and sleeping patterns.

Figure. Median and IQR of CGM Values.



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988-P

Efficacy of the OmniPod® Insulin Management System in Patients with Type 2 Diabetes Previously Treated with Multiple Daily Injections

JENNIFER E. LAYNE, CHRISTOPHER G. PARKIN, HOWARD C. ZISSER, *Billerica, MA, Boulder City, NV*

Continuous subcutaneous insulin infusion (CSII) therapy may be effective for the treatment of insulin-dependent patients with poorly controlled type 2 diabetes. This multi-center, retrospective study assessed glycemic control in patients with type 2 diabetes after 3 months treatment with a tubeless patch pump (OmniPod®, Insulet Corporation, Billerica, MA) compared to previous treatment with multiple daily injections (MDI). The study was conducted in medical practices throughout the U.S. from October 2014 through May 2015. The primary outcome was change in mean HbA1c level from baseline at 3 months post-OmniPod treatment initiation. Secondary outcomes included shifts in HbA1c to target levels, change in mean total daily dose (TDD) of insulin and change in the frequency and severity of hypoglycemic episodes per week. Patients (n=81) with type 2 diabetes treated with OmniPod demonstrated a significant reduction in (mean±SD) HbA1c level from 9.1% ± 1.8 at baseline on MDI therapy to 7.9% ± 1.3 at 3 months (-1.2% ± 1.4; p<0.001). A significant proportion of patients (Δ18.8%) had shifts in HbA1c level to a target of <7.0% (p<0.001). There was a Δ71.4% increase in the number of patients achieving an HbA1c level of 7.0% to <8.0%. The mean TDD of insulin decreased by 27.6 Units from 100.2 ± 54.5 to 72.6 ± 39.3 Units at 3 months (p<0.001). The frequency of hypoglycemic episodes per week decreased from 1.3 ± 2.2 to 0.7 ± 1.0 (Δ46.2%; p=0.004) post-OmniPod treatment. Statistically significant reductions in the severity of hypoglycemic events were also reported (p=0.008). Use of the OmniPod insulin delivery system was associated with clinically meaningful and statistically significant improvements in HbA1c, reductions in daily insulin requirements and reductions in the frequency and of hypoglycemic episodes in patients with type 2 diabetes previously treated with MDI.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

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Blood Glucose Nadirs Do Not Differ Significantly after Various Exercise Bouts under Closed-Loop Conditions

ELIZABETH LITTLEJOHN, KAMURAN TURKSOY, JIANYUAN FENG, LAURETTA QUINN, MOLLY FRUECHT, JULIA RITTHALER, BROOKS HIBNER, JENNIFER KILKUS, DESSI ZAHARIEVA, KRISTEN WROBLEWSKI, ALI CINAR, *Chicago, IL, Toronto, ON, Canada*

Turksoy, et. al developed a multi-variable predictive integrative artificial pancreas (AP) with hypoglycemic warning and automated meal announcements precluding subjects with type 1 diabetes (T1D) from prompting the AP for exercise, sleeping or eating. Because T1Ds are urged to exercise, we sought to test the AP during exercise. 8 subjects (5 male, 3 female, 19 - 27 years) with T1D (ave A1c 7.7%) were studied over 60 hours. Day 1 subjects ate breakfast, then had an aerobic exercise (60-80% heart rate reserve [HHR] used from their VO_{2Max}), ate then had an anaerobic/resistance (AR) exercise (2-3 sets of 8-12 reps, 60-80% rep 1 max). Day 2 they ate breakfast then had AR exercise (same as day 1), ate then had an interval exercise (30-40 min; 5 min warm up, 3 min at 60-70% HRR of VO_{2MAX}, 4 minutes at 85-90% HHR of VO_{2MAX} x 4, with 5 min cool down). Day 3 was identical to day 1. Meals were identical for each subject. Average peak blood glucose (BG) change from baseline, for each exercise and subject were analyzed using repeated measures ANOVA with Greenhouse-Geisser adjustment. No difference in BG was detected across 3 exercises (p=0.11). BGs decreased least with AR exercise. Due to small sample size, a nonparametric Friedman's test confirmed these results (p=0.14). BG pattern for females vs. males differed. Gender difference was almost significant (p=0.06). Differences in gender effect depended on type of exercise. There was no difference between genders with AR exercise, yet there were bigger differences with aerobic and interval exercise. A test of gender by exercise type interaction did not reach significance (p=0.20), likely due to small sample size. Neither group experienced hypoglycemic episodes during or after any exercise. This AP performed safely under various rigorous activities in males and females. Male and female T1Ds respond differently to exercise. More data needs to be generated then compared to BGs under open loop conditions to prove superiority of this AP during varied exercises.

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990-P

Meal Composition Must and Can Be Taken into Account by Automated Correction of Carbohydrate-to-Insulin-Ratio

FLORIAN REITERER, GUIDO FRECKMANN, STEFAN PLEUS, STEFAN WEINERT, LUIGI DEL RE, *Linz, Austria, Ulm, Germany, Indianapolis, IN*

T1DM patients determine their bolus insulin needs using patient and daytime specific values for carbohydrate to insulin ratio (CIR). In standard bolus calculators only the carbohydrate content of the meal is used for determining the insulin requirements, whereas newer research suggests that also fat and protein should be considered. Especially meals with a high fat content reportedly require additional insulin.

A previously published method has been used to determine patient and daytime specific CIR values from recorded data (CGM profiles, bolus insulin and meal carbohydrates - no information about meal composition) of a recent clinical trial over 7 days with 40 patients. During 2 days of the trial the patients ingested a breakfast consisting almost entirely of fast absorbing carbohydrates, whereas for the other 5 days the patient could choose their breakfast composition freely, resulting in significantly higher intakes of fat and protein (high carb breakfast: 80.7% carbohydrates, 10.3% protein, 9.1% fat; average standard breakfast: 42.7% carbohydrates, 15.6% protein, 42.1% fat; % of total meal calories). Using aforementioned method the parameters of a model were adjusted to the clinical data and a patient-specific CIR was calculated from the model parameters for both, the high carb and the standard breakfasts.

The identified CIR values for the high carb breakfast were typically higher than the corresponding CIRs for the standard breakfast, indicating a lower insulin requirement per gram of carbohydrates for the high carb breakfast. On average the CIR for the high carb breakfast was 14.0% higher. The difference in CIRs was found to be highly significant (p=0.0008).

The identified CIR values show that mixed meals require a higher amount of insulin per gram of carbohydrates than meals consisting (almost) only of carbohydrates for a correct glycemic control. The proposed method is able to adjust the insulin needs accordingly.

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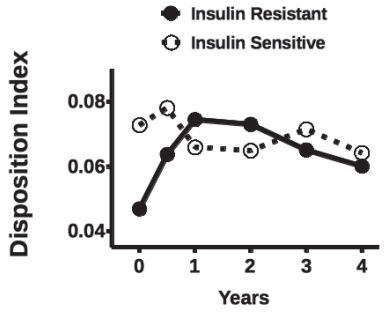
991-P

Blood Glucose Regulatory Capacity Depends Mainly on Initial Beta-Cell Function, Not on Glucotoxicity during Long-Term Insulin Pump Therapy in Type 2 Diabetics

SOO BONG CHOI, EUN SHIL HONG, HYUN-JU AN, YUN-HEE NOH, *Seoul, Republic of Korea, Chungju, Republic of Korea*

By insulin pump (CSII) therapy, hyperglycemia can be controlled to near normal in type 2 diabetics. We wanted to elucidate the changes of beta cell function, insulin sensitivity and disposition function during long-term CSII therapy in type 2 diabetics up to 4 years. We discontinued oral antidiabetic drugs and applied CSII therapy to type 2 diabetics (number, 163 with 56.4% of male; age, 59.7 ± 9.7 years; duration, 11.1 ± 6.9 years; HbA1c 8.9 ± 1.9%; BMI 24.4 ± 3.1 kg/m^2). Blood samplings were performed yearly for 4 years at overnight fasting and 120 minutes after ingestion of a standard mixed meal (500 kcal). Serum C-peptide and glucose, hemoglobin A1c (HbA1c) were measured and C-peptidogenic Index (CI), Matsuda Index (MI) and disposition Index (DI) were calculated. Patients were grouped into high MI (insulin sensitive group) and low MI (insulin resistant group) by mean value of baseline MIs. HbA1c decreased significantly from 8.9% to 6.6% and there were no difference between two groups. In insulin sensitive group, serum C-peptide increased significantly and DI did not change. In insulin resistant group, serum C-peptide did not increase and the DI increased significantly (Figure 1). In conclusion, the capacity of regulating the blood glucose (disposition function) in type 2 diabetes might be affected mainly by beta cell function, and partially by glucotoxicity.

Figure 1. Disposition Index Change for 4 Years by Insulin Pump Therapy in Type 2 Diabetics.



992-P

Safe Automated Insulin Delivery during Daily Living Conditions

ROBERT KIRCHER, DON MATHESON, RICHARD MAUSETH, *Redmond, WA*

The objective of this research is to improve the safety of automated insulin delivery when encountering everyday system incidents such as: sensor changes/calibrations, system startup/shutdown, Continuous Glucose Monitor (CGM) and insulin pump communication errors, infusion set changes, insulin refills and battery changes.

Our new system safety monitor (SSM) includes Boolean mode control logic, which allows hybrid or fully automated closed-loop insulin dosing only when the CGM and pump are operating normally. The system default operating mode is closed loop. The SSM suspends automated insulin delivery and transitions to the user's preprogrammed basal when it detects something is wrong. Automated closed loop insulin delivery resumes when problems are resolved.

In real-time the SSM reads CGM and pump status data, mode and historical glucose data. CGM normal operation depends on the recency, spacing and time span of the sensor glucose data. Pump normal operation is determined by Boolean analysis of status bits read from the pump. Wireless communications faults are detected by monitoring the CGM and pump heartbeat signals.

Forty system incidents, resulting in missed automated insulin doses, occurred in 17 Daily Living clinical studies in the CRC. In each case, because the SSM was not yet implemented, the on site engineer intervened to manually restore closed-loop dosing. We analyzed the 40 system incidents given the SSM module logic design and concluded that 38 (95%) of the incidents would have been detected and the closed loop dosing temporarily suspended by the SSM. The remaining 2 incidents were caused by operator error and not detectable by the SSM.

The retrospective analysis of system incidents in prior clinical studies showed that the SSM would have successfully detected 95% of the system faults and temporarily suspended closed loop dosing. This analysis shows that our fuzzy logic dosing algorithm in conjunction with the SSM, will safely administer automated insulin delivery during daily living conditions.

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993-P

Optimizing Insulin Therapy in Older Adults in Long-Term Care: A Comparative Retrospective Analysis of V-Go vs. Standard of Care (SOC)

ALAN BOONIN, JOSEPH MARTINEZ, BRENDA BALINSKI, JERRY SAUTER, SCOTT ABBOTT, *Dallas, PA, Plainsboro, NJ, Plains, PA, Zionsville, IN*

More than 25% Nursing Home (NH) residents aged 65 years and older have diabetes and evidence supports that patients with poor glycemic control are more likely to experience diabetic complications and higher healthcare costs. This analysis compared the efficacy, glycemic fluctuations and cost impact of two different insulin administration systems in NH patients.

A retrospective study evaluated two groups of 4 patients matched on mean 30-day blood glucose (BG) values to compare the effect of utilizing V-Go vs. SOC. Daily BG readings were obtained by nursing staff at up to 4 time points each day for 8 weeks. Efficacy variables included proportion of Time in Range (100mg/dl-200mg/dl), change in mean daily BG, change in glucose excursions and change in insulin administration.

Significant improvements in BG Time in Range from baseline to endpoint was observed for the V-Go group relative to SOC (59.09% vs. 34.02%; p<0.001). Significant improvements in BG measures were observed at all 4 daily BG testing time points for the V-Go group as well. The number of glucose excursions >200mg/dl was significantly lower with the V-Go group (23.24% vs. 56.77%; p<0.001). Improved mean daily BG (V-Go 159.38mg/dl vs. SOC 223.86mg/dl; p<0.001) was also observed. The calculated A1c, based on the criteria utilizing known BG averages, decreased to 7.2% from 9.4% for the V-Go group (p<0.001). The mean number of unique daily injection sites was 1.0 for V-Go and 6.4 for SOC. Insulin administration costs decreased as calculated by $436/patient/month for V-Go therapy.

Insulin administration with a disposable insulin delivery device can provide improvements in glycemic control and administration costs in older adults with insulin-dependent diabetes in the NH setting. Given these findings larger controlled studies are needed to fully evaluate the use of V-Go in this patient population.

994-P

Better Postprandial Glucose Control with a New Closed-Loop System as Compared with Open-Loop Treatment in Patients with Type 1 Diabetes

PAOLO ROSSETTI, CARMEN QUIRÓS, VANESSA MOSCARDÓ, ANNA COMAS, MARGA GIMÉNEZ, FRANCISCO JAVIER AMPUDIA-BLASCO, FABIÁN LEÓN, ESLAM MONTASER, IGNACIO CONGET, JORGE BONDIA, JOSEP VEHÍ, *Gandia, Spain, Barcelona, Spain, Valencia, Spain, Girona, Spain*

Postprandial period (PP) control is still a challenge for closed-loop (CL) control algorithms. Although recent at-home studies have demonstrated better daytime glucose control with CL systems as compared to pump therapy, few studies with inconsistent results have investigated systematically the PP.

This study compares randomly, in subjects with type 1 diabetes (T1D), a new developed CL algorithm implementing sliding mode reference conditioning (SMRC) with current open-loop (OL) during the PP.

20 T1D subjects (F/M 13/7, disease duration 22.6±9.9 y, A1c 7.7±0.7%) underwent an 8-hour standardized mixed meal test (60g carbohydrate, CH) on 4 occasions, after normalization of plasma glucose (PG) to euglycemia using an iv feedback insulin infusion. They wore Paradigm Veo® devices and two continuous glucose monitors (CGM, Enlite-2®). In addition to CGM, PG was measured every 15 min. On 2 occasions (CL1/CL2), after a meal-announcement a bolus was given followed by 15-min based-on-CGM adjustments of basal rate. Alternatively, in OL1/OL2 usual pump therapy was used and boluses based on individual insulin/CH ratios. In case of hypoglycemia (PG<70mg/dl), oral glucose (OG, 15g/15 min) was given until recovery.

CL improved PG control in the early and late PP (CL1=CL2<OL1<OL2; mean±SD, p<0.01, all): $PG_{0\text{-}8h}$ 123±47 and 125±44 vs. 152±53 and 159±54 mg/dl; PG_{max} 180±48 and 186±42 vs. 212±48 and 222±47 mg/dl. Time-in-range (70-180mg/dL) was greater with CL 381±97 vs. OL 307±120 min (p=0.001). Time-below 70mg/dl was not significantly different (CL 30±42 vs. OL 18±37 min), but need for OG was higher with CL (40.0% vs. 22.5% of tests, p=0.017), especially in the late PP (between 3-8h). However, the mean rescues/test (range) was low in both: CL 0.825 (0-4); OL 0.475 (0-6).

In conclusion, our CL algorithm controls effectively and consistently PP excursions achieving euglycemia in the postabsorptive state without a clinically meaningful increased risk of hypoglycemia.

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995-P

Patient User Experience Evaluation of Bolus Patch Insulin Delivery System

VIVIEN ZRAICK, DARLENE DREON, RAMACHANDRA NAIK, DAVID SHEARER, SAM CRAWFORD, JOHN BRADFORD, BRIAN LEVY, *Redwood City, CA, Wayne, PA*

This was a U.S.-based, patient user experience evaluation (treatment satisfaction and adoption barriers) of an FDA-cleared, novel, bolus patch insulin delivery system (Calibra Medical, Inc.). A total of 44 adult diabetes patients (40 T2D and 4 T1D), median age 57 years (range 22-75), mean A1c 8.5%, and on meal-time rapid-acting insulin, used bolus patch in lieu of their current bolus injection device (75% pen and 25% syringe users; mean duration of use: 6 years) for a period of 60 days. Patients responded to insulin usage questionnaires at baseline, and after 1, 4, and 8 weeks of bolus patch usage. Responses were coded on a scale of 1-5 (1=not at all likely/satisfied; 5=extremely likely/satisfied). No clinical endpoints were specified. After 60-day usage, 86% of patients were extremely/very satisfied with the bolus patch system, 79% were extremely/very likely to ask their HCP for a prescription, and 74% were likely to use bolus patch as a replacement (60%) or in addition to (14%) their current delivery device. More than half the patients claimed that they would dose with the bolus patch more often than with their previous device, and >50% of patients also cited instances where they dosed with bolus patch and probably would not have dosed using their pen/syringe; most often noted were occasions outside the home. The bolus patch let patients dose discreetly in public (98%), made it easier to dose insulin (95%), do a better job following insulin regimen (88%), worry less about forgetting insulin (88%), have a less stressful life (88%), and avoid painful mealtime injections (76%). Most patients reported short learning curve and used the device without difficulties. While there were some reported initial adoption issues related to preparation of the device for use, wearability, skin sensitivity, and/or mechanical issues, these improved with ongoing patient education and experience. Overall, the bolus patch usage led to high patient satisfaction, and helped overcome usage barriers associated with multiple daily insulin injections.

996-P

Effect of Meal Detection Suppression on Postprandial Glycemic Excursion in Fully Closed-Loop Artificial Pancreas with Unannounced, Unscheduled Large Meals

GREGORY P. FORLENZA, FAYE CAMERON, NIHAT BAYSAL, BRUCE A. BUCKINGHAM, PAULA CLINTON, DAVID LAM, CAROL LEVY, CAMILLA LEVISTER, TRANG T. LY, DAVID M. MAAHS, LAUREL H. MESSER, STEPHEN D. PATEK, EMILY WESTFALL, YAN YAN XIE, B. WAYNE BEQUETTE, *Aurora, CO, Palo Alto, CA, Troy, NY, Stanford, CA, New York, NY, Charlottesville, VA*

A fully closed loop artificial pancreas (AP) using the multiple model probabilistic predictive control (MMPPC) framework was tested at 3 hotel sites on 15 subjects (87% F; 14-51 y/o) for a total of 31 days. MMPPC is a unique implementation of model predictive control (MPC) using a continuous, rather than binary, detection of unannounced meals and their size. It uses data about meal times from the National Health and Nutrition Examination Survey, and about meal shapes from previous triple tracer studies. Patients often perform continuous glucose monitoring (CGM) calibration with pre-prandial BG testing. To avoid misinterpretation of a calibration BG rise as a prandial glycemic excursion, we suppressed our meal detection for 30 minutes after calibration, creating the possibility for delayed meal bolus delivery and resultant elevated glycemic excursions. We analyzed the MMPPC data set to evaluate the validity of this concern.

Among substantial meals (>20 g of CHO with foods selected as desired by study subjects) there were no significant differences for post-prandial glycemic excursion between those not receiving and receiving pre-prandial calibration for breakfast (CGM glucose Avg: 178.1±36.7 vs. 181.7±33.5 mg/dL, p=0.82; CGM glucose Max: 244.8 vs. 241.5 mg/dL, p=0.90; AUC>180 mg/dL: 4475 vs. 3588 min*mg/dL, p=0.70) or dinner (CGM glucose Avg: 176.9±40.1 vs. 170.8±38.0 mg/dL, p=0.70; CGM glucose Max: 237.1 vs. 229.7 mg/dL, p=0.79; AUC>180 mg/dL: 6290.3 vs. 6097.4 min*mg/dL, p=0.96). There was no significant difference in the time to insulin delivery when the pre-prandial glucose was not used for calibration or was used for calibration, (28.3 vs. 40.1 min, p=0.072). We had anticipated that suppression of meal recognition for 30 minutes (with sensor calibration) would cause a deterioration in post-prandial glucose control. In this setting MMPPC post-prandial glucose control was unaffected by a pre-meal sensor calibration.

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997-P

Effects of Glucose Target on the Performance of a Bihormonal Bionic Pancreas

FIRAS ELKHATIB, LAYA EKHLASPOUR, COURTNEY BALLIRO, RAJENDRANATH SELAGAMSETTY, ARYAN ESMAEILI, MALLORY HILLARD, DEBBIE MONDESIR, EDWARD R. DAMIANO, STEVEN J. RUSSELL, *Boston, MA*

We previously demonstrated the safety and effectiveness of an automated bihormonal bionic pancreas (BP) delivering insulin and glucagon with a glucose target of 100 mg/dl. We hypothesized that raising the glucose target would increase mean glucose while reducing hypoglycemia and/or reducing glucagon usage. We performed a random order cross-over study comparing glycemic regulation by the bihormonal BP at three glucose targets (100, 115, and 130 mg/dl) and also contrasting each with usual care (conventional insulin pump therapy). Subjects went about their daily routines with no limitations on diet or exercise during each 3-day test period.

Different BP glucose targets (100, 115 mg/dl, and 130 mg/dl) were associated with different mean CGM glucose levels (136±14 mg/dl, 146±15 mg/dl, and 156±12, p≤0.016 for each comparison), but no significant reduction in percent time <60 mg/dl (0.8±1.1, 0.9±1.2%, 0.6%±1.0, p≥0.37 for each comparison). However, there was a significant reduction in glucagon total daily dose (8.3±3.0, 5.3±2.3, 2.2±1.2 µg/kg/day, p≤0.0012 for each comparison). The mean CGM glucose level in the usual care arm, 158±31 mg/dl, was higher than that of the BP arm with the target of 100 mg/dl (p=0.0028), but was not different than the BP arms with targets of 115 mg/dl (p=0.073) and 130 mg/dl (p=0.85). Hypoglycemia in the usual care arm did not differ from any of the BP arms (p≥0.18 for each comparison). Mean daily nausea score on a 10 cm visual analog scale was low in all arms, but was lower as the BP target was increased from 100 mg/dl (1.2 cm), to 115 mg/dl (0.8 cm, p=0.25 vs. 100 mg/dl), to 130 mg/dl (0.4 cm, p=0.0013 vs. 100 mg/dl; p=0.035 vs. 115 mg/dl). Nausea was lower in the usual care arms (0.3 cm) than in all BP arms (p≤0.040 for each comparison).

Increasing the glucose target of the bihormonal bionic pancreas increased the mean glucose without significantly reducing already low levels of hypoglycemia, but reduced glucagon usage and further reduced low levels of self-reported nausea.

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998-P

Incremental Benefits of Predictive vs. Responsive Low Glucose Suspension Strategies in Automated Insulin Delivery Systems

CHANTAL M. MCMAHON, ALEX ZHONG, BOYI JIANG, WILFREDO RODEZNO, KEVIN VELADO, MICHAEL STONE, PRATIK J. AGRAWAL, JOHN B. WELSH, FRANCINE R. KAUFMAN, *Northridge, CA*

Two distinct commercially-available systems, with different strategies for suspending insulin delivery, were compared with respect to sensor glucose (SG) parameters reflecting hypoglycemic and hyperglycemic exposure. The MiniMed 640G system's predictive low glucose management (PLGM) feature uses existing and predicted SG values with a 30-min prediction horizon to stop insulin delivery before hypoglycemia occurs and restart it upon recovery. The MiniMed Veo system's low glucose suspend (LGS) feature stops insulin delivery in response to a SG value at or below a pre-specified threshold. Hypoglycemia was defined as SG ≤70 mg/dL and hyperglycemia as SG ≥300mg/dL. Within-subject comparisons were made using paired t-tests. We identified 851 people who uploaded ≥7 days of data from each system; all had been using Veo before switching to 640G. With Veo, 86% of the users enabled the LGS feature at any time; the average use was 82±30% of the time. All of the 640G users enabled one or more of its insulin management features; the average use was 88±24% of the time. After switching, users had less time in hypoglycemia, and their hypoglycemic excursions were fewer and less severe as measured by AUC. Hyperglycemic parameters also improved after switching (Table). Advanced insulin management features such as PLGM may improve glycemic outcomes in insulin-requiring patients.

Table. Glycemic Parameters with Responsive (Veo) and Predictive (640G) Insulin Delivery Strategies.

Parameter		Veo	640G	p
Hypoglycemia	Duration, min/day	68	43	<0.001
	AUC, mg/dL × day	0.44	0.32	<0.001
	Excursions per day, n	1.13	0.87	<0.001
Hyperglycemia	Duration, min/day	50	46	0.01
	AUC, mg/dL × day	2.47	2.06	<0.001
	Excursions per day, n	0.54	0.48	<0.001

The 640G and Veo devices are investigational devices not approved for sale in the United States.

Supported By: Medtronic

999-P

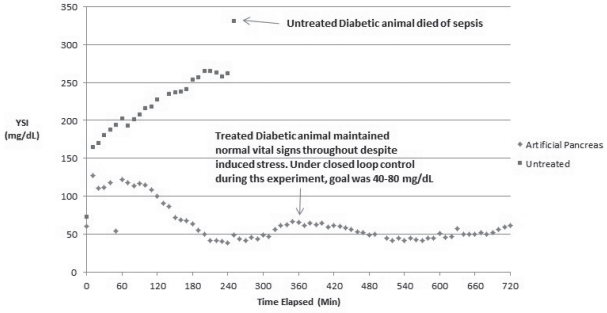
Performance of an Artificial Intelligenced-based Artificial Pancreas in Swine Model of Stress-induced Hyperglycemia

LEON DEJOURNETT, JEREMY DEJOURNETT, *Asheville, NC*

Effective glucose control in the Intensive Care Unit (ICU) has the potential to save 100,000 lives and at least $5 billion annually in the U.S. A closed loop glucose control system, or artificial pancreas for use in the ICU does not currently exist. We have created an Artificial Intelligence (AI) Based closed loop glucose controller for use in the ICU setting. An early stage prototype of this system was tested in a swine model of stress induced hyperglycemia. Stressors included acid lung aspiration, endotoxin infusion, high dose steroids and glucose infusion. Two of the animals were given Octreotide (Sandostatin) to induce a type 1 diabetic state. The glucose sensors used included one in the carotid artery (Data Sciences International = DSI) and two interstitial (Dexcom), all of which were calibrated using YSI values. The 3 sensor values were averaged to produce a final glucose value for the control algorithm. The results from the two "diabetic" animals are noted in the Figure.

This animal study provides proof of concept of an Artificial Intelligence based glucose controller for use in the ICU setting. In order to enhance reliability and safety, a multi-sensor array such as used in this study should be considered. After the desired range of 40-80 mg/dL was first reached, 90-100% of all subsequent values remained in the desired range. The modified DSI sensor had R values as high as 0.95 vs. YSI values.

Figure. Stress Induced Hyperglycemia—Untreated vs. Artificial Pancreas.



1000-P

Improved Glycemic Control in Patients with Type 2 Diabetes Switching to the V-Go® Insulin Delivery Device: A Prospective Study Utilizing Continuous Glucose Monitoring

OPDADA ALZOHAILI, SHEILA WHELAN, AHMAD YUSUF SOLAIMAN, NADIA ALDHALIMY, SCOTT ABBOTT, LEON SHI, *Dearborn, MI, Zionsville, IN, Princeton Junction, NJ*

Continuous glucose monitoring (CGM) is a valuable tool to assess if changes in therapies lead to improvements in glucose control beyond that provided by A1c alone. This study evaluated the change in glycemic control using CGM after patients switched to V-Go from standard insulin injection regimens. A prospective study was designed to evaluate patients with inadequate glucose control on standard insulin injections switching to V-Go. Inclusion criteria were patients with type 2 diabetes, using long-acting insulin or multiple daily injections, with an A1c ≥7%. Patients were instructed to use CGM for at least 72 hrs while on baseline therapy and again after 3 months. Insulin dosing and titration followed standard clinical practice. All medications and supplies were obtained by the patient through usual care. Twelve patients having valid CGM measures and meeting inclusion criteria were evaluated. Patients had a baseline A1c of 8.5%, body weight of 219.6 lbs (BMI 36.5) and had diabetes for 16 yrs. The mean V-Go treatment duration was 3.5 mos. Switching to V-Go resulted in improved glycemic control (Table). A paired T-test shows a significant (P=0.0243) change in glucose of -37.8 mg/DL (corresponds to A1c -1.3%). Patients switching to V-Go had improved average daily glucose, lower and less frequent hyperglycemia, and an increased time in range.

Table.

BG (mg/dl) assessments using CGM	Average Glucose Value	Highest Glucose Value	Lowest Glucose Value	Measures Above 140mg/dl	Measures Within 100-140 mg/dl	Measures Below 100 mg/dl	AUC Above 140 mg/dl	AUC Below 100 mg/dl
Pre-V-Go	198.4	333.6	93.9	71.0%	21.33%	7.67%	51.14%	0.11%
V-Go	160.6	309.0	58.6	58.92%	36.5%	4.58%	35.59%	0.67%

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ADA-Supported Research Moderated Poster Discussion

For author disclosure information, see page A696.

1001-P

Evaluating V-Go® in Patients 65 Years of Age or Older with Poorly Controlled Diabetes: A Health Outcome and Economic Analysis from an Endocrine and Diabetes Specialty System

DAVID SUTTON, CHARISSA HIGDON, MARK CARMON, SCOTT ABBOTT, *Jacksonville, FL, Bridgewater, NJ, Zionsville, IN*

Evidence supports that older patients with poor glycemic control are at increased risk for diabetic complications. A retrospective analysis evaluated patients ≥65 years of age with poorly controlled diabetes being switched to the V-Go® Disposable Insulin Delivery Device (V-Go) to improve glycemic control and reduce cost. An electronic medical records database from a large diabetes system was queried. Patients age ≥65 years old that were switched to insulin therapy with V-Go from existing therapy regimens. The efficacy variable was the % change in A1c from baseline to second follow up visit. Cost of therapy for patients on insulin included cost of concomitant medications and mode of insulin delivery. Thirty two patients were identified with 26 patients having at least two follow up visits. At baseline, patients had a mean A1c of 9.1% SD (±2.08), mean weight of 91 kg±21.22, a mean insulin total daily dose (TDD) of 81 U/day (0.84U/Kg) and a pharmacy cost of $1,009 per patient per month (PPPM). At the second lab appointment (mean 156 days, SD 52.9) on V-Go, 26 patients achieved an A1c reduction of 1.4% ((±1.57, 95% CI -0.861, -2.00; p<0.001). Sixty-two percent of these patients achieved an A1c of ≤ 8%. Despite the significant improvement in A1c a modest +2.7 kg change in weight was observed. Importantly, there was no increase in patient-reported hypoglycemic events for the population. For those patients on insulin, switching to V-Go resulted in a significant reduction in TDD of 19% (95% CI 3.35, -27.08; p=0.013) that was a calculated savings of $255 PPPM in direct pharmacy cost. Patients ≥65 with poor diabetes control and switched to V-Go therapy achieved significant A1c improvement with no increase in hypoglycemic events. The majority of patients achieved the HEIDIS quality goal of an A1c ≤8%. Patients of Medicare age and on insulin therapy had an overall reduction in cost with V-Go therapy that could support better adherence to therapy.

Supported By: Valeritas, Inc.

1002-P

Retrospective Evaluation of an Evidence-based Equation for Insulin Dosing Accounting for Exercise and Alcohol

DANIELLE GROAT, MARIA ADELA GRANDO, GARRICK WALLSTROM, BITHIKA THOMPSON, MARY E. BOYLE, MARILYN BAILEY, CURTISS B. COOK, *Scottsdale, AZ*

iDECIDE (iD) is an evidence-based decision aid that accounts for exercise, alcohol and carbohydrate (CHO) loads in order to recommend rapid-acting insulin boluses to improve postprandial blood glucose (pBG) control. We recruited 9 subjects with type 1 diabetes on insulin pump therapy to retrospectively evaluate the prandial insulin dose recommendations of iD against those from the insulin pump's bolus wizard and against subject's self-dosing choices. Subjects reported exercise performed and alcohol consumed for 30 days, and pump data from the corresponding timeframe was downloaded. A prandial insulin dose recommendation outperformed if it could lead to a closer-to-target 3-hour pBG level. Two doses were considered equivalent if there was a difference of less than 10%. In 713/1033 (69%) recorded pump events iD suggested an equivalent prandial dose as the pump. In 17% of events iD outperformed the pump while the pump outperformed iD in 13% cases. In 117/198 (59%) cases iD and the subjects had equivalent boluses. iD outperformed the subjects in 36% of the cases while the subjects outperformed iD in 2% of the cases. In 99/101 (98%) exercise events iD appropriately advised on insulin and CHO. In 30/48 (63%) alcohol events iD appropriately advised on insulin. We conclude that the iD algorithm may provide enhanced decision making with regards to prandial insulin dosing compared to conventional methods, particularly when incorporating complex life-style choices (exercise, alcohol) into the application. The complicated nature of real-life data required new approaches to data collation and analysis for measuring bolus calculator performance.

Supported By: National Library of Medicine

1003-P

Effect of Insulin Delivery with V-Go® in a Military Disease Management Health Clinic

JILL F. SCHRAMM, JUDY E. CHING, EMILY BANKHEAD, CARLA NIKKEL, *Colorado Springs, CO, Edmond, OK*

As diabetes progresses in patients with type 2 diabetes, blood glucose control becomes more difficult to achieve. Insulin therapy is often necessary but can be challenging for patients requiring basal and prandial coverage. Addressing the manner in which insulin is delivered may impact efficacy and prove beneficial in patients not well controlled on current insulin therapies. No data has been published to date on the use of V-Go® Disposable Insulin Delivery Device in a military system. A retrospective analysis was conducted in 10 patients with type 2 diabetes switched from their previous insulin regimens to insulin delivery with V-Go after two follow-up A1c results were captured. All patients had previously administered basal-only insulin therapy (4 patients) or basal-bolus therapy (6 patients) with or without concomitant antihyperglycemic agents and were not well controlled (A1c > 7.0%). Mean ± SD baseline characteristics were age 62 ± 11 years, weight 177 ± 30 lbs, duration of diabetes 14 ± 8 years, and A1c 8.8 ± 1.0%. Baseline mean (range) insulin doses were 66 (32-95) total units/day and 50 (22-72) basal units/day. Effect of V-Go was evaluated following a mean duration of use of 210 ± 52 days. A1c was significantly improved to 8.0 ± 0.7% (p=0.032) on V-Go. Total insulin dose was reduced by a mean of 21 ± 24 units/day (p=0.021) and the daily basal dose was reduced by a mean of 23 ± 16 units/day (p=0.001). No significant change from baseline was observed for body weight (177.4 lbs at baseline compared to 178.0 lbs, p=0.773). Delivery of insulin with V-Go resulted in improved A1c with a lower insulin requirement and should be considered as an option and readily accessible for insulin therapy in patients receiving diabetes care from military clinics.

1004-P

Insulin Pump Use in Young Children with Type 1 Diabetes (T1D): Sociodemographic Factors and Parent-Reported Barriers

PERSIS V. COMMISSARIAT, CLAIRE T. BOYLE, KELLEE M. MILLER, MANASA G. MANTRAVEDI, DANIEL J. DESALVO, WILLIAM V. TAMBORLANE, BARBARA J. ANDERSON, LINDA A. DIMEGLIO, LORI M. LAFFEL, *Boston, MA, Tampa, FL, Indianapolis, IN, Houston, TX, New Haven, CT*

Unique challenges to managing T1D exist in very young children. Continuous subcutaneous insulin infusion (CSII) pumps for young children can overcome some challenges and improve health outcomes, yet universal uptake is lacking. Reasons for not using CSII in young children are not well-described.

Survey data from the T1D Exchange clinic registry from parents of youth <7 years old (N=387) with T1D for ≥1 year identified barriers to CSII use (all data mean±SD) (age 4.7±1.2 y, T1D duration 2.3±1.0 y, A1c 8.1±1.0%, 45% female, 78% white). Data from parents of current pump users (n=261) were compared to non-users (n=126).

Pump users had longer T1D duration (2.4±1.0 yrs vs. 2.0±0.9, p<0.001), and were more likely to be female (73% vs. 63%, p=0.04), live in homes with annual household incomes ≥$75,000 (79% vs. 59%, p<0.001), and use continuous glucose monitors (43% vs. 13%, p<0.001). Non-users were more likely to report having a DKA event in past 3 months (10% vs. 4%, p=0.03). There were no significant differences in age and A1c. Parent-reported barriers to CSII use appear in the Table. Major concerns with CSII fell into 3 themes: physical interference, therapeutic effectiveness, and financial burden.

Understanding perceived barriers to CSII use among parents of young children with T1D may inform future interventions to improve the uptake of CSII and optimize health outcomes in this group.

Table. Parental-reported Reasons for Not Using CSII Therapy.

Concern	Percent found Somewhat Important to Important
Uncomfortable to wear	74%
Interference with sports and activities	65%
Using the insertion sets/tubing	63%
Low blood sugars when using pump	60%
Having a device on body	60%
Pump would be too big	56%
Skin reactions from the insertion site/adhesive	54%
High blood sugars when using pump	53%
Pump too expensive	44%
Pump too complicated for family/other care providers to use	43%
Insurance does not cover pump	35%
Not enough advice/guidance from HCP on how to use pump	25%

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

1005-P

Do Type 1 Diabetes Patients Really Want an Artificial Pancreas?

SYLVIA FRANC, ILHAM XHAARD, LAURENT ORLANDO, MOUNA EL MAKNI, MARIE-HÉLÈNE PETIT, CAROLINE RANDAZZO, GUILLAUME CHARPENTIER, *Corbeil-Essonnes, France, Evry, France*

It is accepted that the artificial pancreas (AP) could provide a solution to the constraints currently imposed upon patients presenting type 1 diabetes (T1D). But how many patients would wish to have an AP? During an informa-

For author disclosure information, see page A696.

tion forum on AP, 101 T1D (67% patients on insulin pump therapy, mean age 50 ± 17 years, age at diagnosis 21.3 ± 14 years, HbA1c 7 ± 0.9%) completed 2 identical questionnaires before and after presentation of AP (continuous glucose measurement, patch pumps, smartphone management software, human machine interactions with tracking of meals and physical activity, and monitoring software). Before the information, 42% patients imagined that AP involves grafting of an artificial organ, 27% imagined a device carried on the body like a pump, and 18% thought it referred to a smartphone application. When asked if they would like to have an AP, 56% gave no answer while 40% said yes vs. respectively 27% and 67% after the information session. 32, 35 and 19% of patients estimate the time to availability of Aps at under 2, 5 and 10 years respectively. Logistical regression analysis suggests that the desire to have an AP is determined by 2 factors: the recency of onset of T1D (OR=0.94/year of duration p=0.014) and ongoing treatment with pump therapy vs. multiple daily injections (OR=0.26; p=0.058). Thus, agreeing to carry a pump or a pump patch, or to use a smartphone to manage the AP (respectively OR=7.73; p=0.03, OR=9.10; p=0.003, OR=5.01; p=0.038) were all positive factors for using an AP. However, dissatisfaction with current therapy, the hope of improved HbA1c levels or decreased risk of hypoglycaemia or associated complications, freedom or comfort, and the length of time needed to develop the device, did not appear to be significantly correlated with hopes about AP. Of 101 T1D patients, 67% expressed a wish to use such a device, while 27% continued to have doubts and 6% rejected the idea. In the real world these proportions could be slightly less, as in our sample there was a high proportion of patients treated with insulin pump.

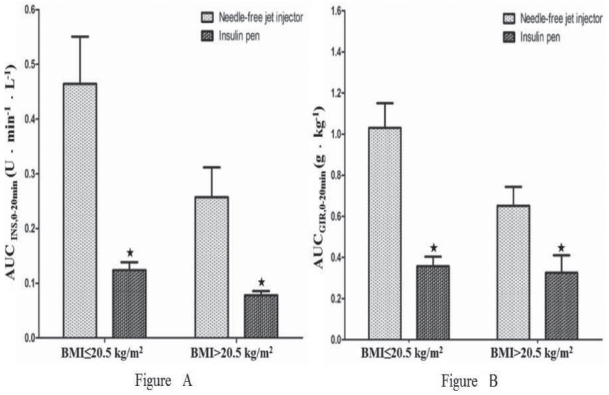
1006-P

Lispro Injected by Jet Injector Benefit Nonobese

HU JINBO, QIFU LI, SHUMIN YANG, *Chongqing, China*

Administration of aspart by jet injector results in a faster correction of hyperglycaemia in overweight or obese patients with diabetes. The aim of this study is to evaluate the pharmacokinetic and pharmacodynamic (PK-PD) profiles of insulin lispro administered by jet injector in nonobese subjects.A randomized, double-blind, double-dummy, cross over study was performed. Eighteen healthy nonobese volunteers (BMI<24 kg/m^2, and median BMI was 20.5 kg/m^2) were recruited. Lispro (0.2 units/kg) was administered by jet injector or by conventional pen. Seven-hour euglycemic clamp tests were performed. A larger area under the curve (AUC) was observed for the interval 0 to 20 minutes for insulin concentration and glucose infusion rate (GIR) after lispro was injected by the jet injector compared to the insulin pen (0.36±0.24 vs. 0.10±0.04 U·min^{-1}·L^{-1}, P<0.001 for AUC_{INS}, 0-20 min; 0.84±0.37 vs. 0.34±0.20 g·kg^{-1}, P=0.023 forAUC_{GIR}, 0-20 min). AUC_{INS}, 0-20 min and AUC_{GIR}, 0-20 min were negatively correlated with BMI (r=-0.58, P=0.012 for AUC_{INS}, 0-20 min; r=-0.48, P=0.045 for AUC_{GIR}, 0-20 min). There were no differences in total insulin exposure and hypoglycemic effects between the two devices. In nonobese subjects, administration of lispro by a jet injector generates improved early PK-PD profiles. Early potency of lispro administered by the jet injector is weakened with the increment of BMI in nonobese subjects.

Figure. Early PK-PD Profiles ($AUC_{INS,0\text{-}20min}$ and $AUC_{GIR,0\text{-}20min}$) for Lispro Administered by the Needle-free Jet Injector and Conventional Pen in Subgroups of Participants with a BMI Below and Above 20.5 kg/m^2.



Supported By: National Key Clinical Specialties Construction Program of China; National Natural Science Foundation of China (81170751, 81370954, 81200294)

1007-P

Evaluating the Impact on Diabetes Control with V-Go® for Patients with Diabetes Not Achieving Optimal Control: A Retrospective Cohort Analysis in a Large Endocrine and Specialized Diabetes System

DAVID SUTTON, CHARISSA HIGDON, MARK CARMON, SCOTT ABBOTT, *Jacksonville, FL, Bridgewater, NJ, Zionsville, IN*

The purpose of this retrospective analysis was to evaluate the impact on glycemic control of switching to the V-Go® Disposable Insulin Delivery Device (V-Go) for patients with diabetes mellitus (DM) that are sub-optimally controlled. Using an electronic medical records database from a large specialty clinical practice a query was performed to identify patients not achieving a target A1c ≤ 7.0%. Sub-optimally controlled patients with diabetes changed to V-Go between August 2012 and August 2015 were assessed. All patients had a valid baseline and at least one follow-up visit (FV) with a documented A1c measure. A1c, weight, therapy including insulin dosing and reported hypoglycemia were collected at baseline and subsequent office visits. Seventy-six patients had a first follow-up visit (FV1) and to date, 62 patients had a second visit (FV2), 50 patients had a third visit (FV3) and 39 patients had a fourth visit (FV4). The mean age was 63 years, mean weight was 93 kg, the mean BMI was 32, and the mean baseline A1c was 9.7% for the overall population. Significant A1c reductions at FV1, FV2, FV3, and FV4 were observed for the all patients (p<0.0001). After a mean duration of 161 days on V-Go, the mean change [95% CI] in A1c from baseline for the total population was -1.7% [-1.2, 2.1]. For patients previously on insulin at baseline, a 27% reduction (82 to 60 U/day) in total daily insulin and a 24% reduction in basal insulin (46 to 35U) from baseline was observed. The total population experienced a mean increase in weight of approximately 3kg (p=0.002). Substantial improvements in glycemic control were observed with no increase in the overall incidence of reported hypoglycemia. V-Go provided an effective and safe method of insulin delivery that was sustainable for many patients with uncontrolled diabetes regardless of baseline therapy.

Supported By: Valeritas, Inc.

1008-P

Insulin-Only Bionic Pancreas: Preliminary Results

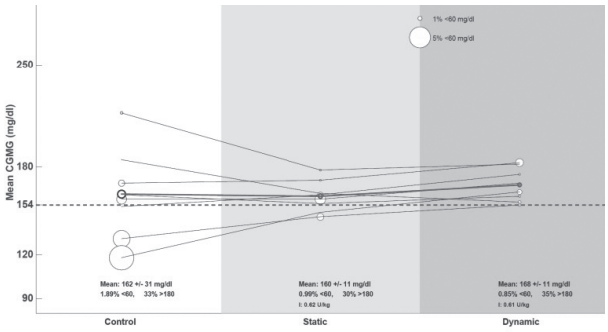
KOREY K. HOOD, BRUCE A. BUCKINGHAM, TRANG T. LY, PAULA CLINTON, ELIANA FRANK, SARAH HANES, RAJ SELAGAMSETTY, FIRAS EL-KHATIB, EDWARD R. DAMIANO, *Stanford, CA, Boston, MA*

The Bionic Pancreas (BP) is a dual-hormone (insulin and glucagon) closed-loop system. We tested an insulin-only BP (BPIO) to assess glycemic setpoints and human factors (HF) outcomes in an outpatient setting.

The initial cohort of 8 participants (4 females) had a mean age of 31 y (20-45 y), A1c of 7.6% (6.6-9.1%), and daily insulin dose of 0.6 u/kg (0.4-1.0). Participants had 5 days of usual care, 5 days on BPIO with an individualized static setpoint of 115 or 130 mg/dl, followed by 5 days of using a dynamic setpoint that automatically varied within 115-145 mg/dl depending on risk for hypoglycemia. HF testing was done at enrollment and study completion; a focus group was done at study completion. HF testing included validated surveys on well-being, diabetes distress, burden from diabetes devices, and treatment satisfaction. Glycemic outcomes are presented in the Figure.

There was less glycemic variability (inter- and intra-subject) and hypoglycemia with both static and dynamic setpoints compared to the control period; mean glucose was unchanged. HF testing showed no declines on well-being, diabetes distress, and satisfaction; improvement in less burden from diabetes devices (effect size = 0.41). Participants viewed the BP working best at night and wished for more manual inputs during the day. In the focus group, 7 of 8 reported they would go home with the BP as is. In sum, the BPIO demonstrated preliminary safety and no increased risk of diabetes burden or distress.

Figure.



Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

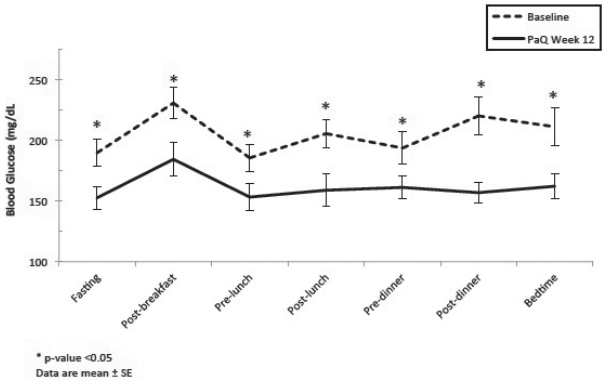
1009-P

PAQ® 3-Month Observation Study in Adults with Type 2 Diabetes

JULIA K. MADER, LESLIE C. LILLY, FELIX ABERER, TINA POETTLER, SEBASTIAN BECVAR, CHRISTIAN LANZ, MICHAEL TRAUTMANN, THOMAS R. PIEBER, *Graz, Austria, Concord, MA, Hamburg, Germany*

PAQ® (CeQur SA) is a simple 3 day continuous subcutaneous insulin delivery device which provides set basal rates and bolus insulin on demand. In this single-arm study, type 2 diabetes (T2D) patients (A1c ≥7.0 ≤11.0%) on ≥ 2 insulin injections/day were enrolled to assess the performance and safety of PAQ. The study comprised 3 periods: baseline (1 week current insulin therapy), transition to PAQ (1-2 weeks), and PAQ treatment (12 weeks). Performance was assessed by change in: A1c, venous fasting blood glucose (VFBG), 7-point self-monitored blood glucose (SMBG), total daily insulin dose (TDD) and body weight after 12 weeks of PAQ. Safety endpoints included hypoglycemia (BG ≤70 mg/dL) and adverse device effects. Twenty adults (age 63 ± 7 y, 15% female, BMI 32.2 ± 3.7 kg/m^2, diabetes duration 15 ± 7 y, A1c 8.6 ± 1.1%) were enrolled and 17 completed (2 terminated early for personal reasons, 1 due to protocol violation). Transition to PAQ with first basal rate selected occurred in 76% of patients. After 12 weeks of PAQ, A1c was reduced by 1.4 ± 0.9% (p≤0.0001) and VFBG by 30 ± 54 mg/dL (p=0.03). Compared to baseline SMBG changed significantly (Figure), TDD increased by 14.3 U (p<0.01) while body weight was stable. 5 patients had mild to moderate catheter site reactions, 1 had mild skin irritation. No patient experienced severe hypoglycemia. T2D patients were safely transitioned from multiple insulin injections to PAQ and achieved significantly improved glycemic control.

Figure. 7-point SMBG Profile.



Supported By: CeQur

1010-P

Efficacy of the OmniPod® Insulin Management System on Glycemic Control among Patients with Type 1 Diabetes Previously Treated with MDI or CSII

JENNIFER E. LAYNE, CHRISTOPHER G. PARKIN, HOWARD C. ZISSER, *Billerica, MA, Boulder City, NV*

This multi-site, retrospective study evaluated glycemic control in patients with type 1 diabetes (n=873) after 3 months treatment with a tubeless patch pump (OmniPod®, Insulet Corporation, Billerica, MA) compared to prior treatment with multiple daily injections (MDI) (78.1%) or continuous subcutaneous insulin infusion (CSII) (21.9%). The primary outcome was change in mean HbA1c level from baseline at 3 months post-OmniPod treatment initiation. Secondary outcomes included shifts in HbA1c to target levels, change in mean total daily dose (TDD) of insulin and change in the frequency and severity of hypoglycemic episodes per week. HbA1c was significantly lower at 3 months post-OmniPod treatment compared to MDI (mean±SD): -0.3%±1.3, -0.4%±1.4, -0.8%±1.3 and -0.6%±1.3 for pediatric, adolescent, adult and total, respectively (p=0.002 to p<0.001). Similar improvements in HbA1c were demonstrated compared to prior CSII treatment: -0.3%±0.8, -1.1%±1.6 (p<0.01), -0.4%±1.1 (p<0.001), and -0.5%±1.1 (p<0.001) for pediatric, adolescent, adult and total, respectively. The decrease in HbA1c at 3 months for the total population was -0.6%±1.3 (p<0.001). Overall, there were significant (p<0.001) shifts in HbA1c levels of poor control to better control. There was a Δ37.9% increase in the proportion of patients ≥18 years and a Δ39.3% increase in those <18 years achieving ADA treatment targets. There was a Δ16.4% decrease in TDD of insulin at 3 months for the total population (p<0.001). The frequency of self-reported hypoglycemia decreased significantly (p<0.001) by 1.0±2.4 episodes per week post-OmniPod treatment. The severity of hypoglycemic episodes was also significantly lower (p<0.001). Use of the OmniPod insulin management system was associated with clinically meaningful and statistically significant improvements in HbA1c, reductions in daily insulin requirements and reductions in the frequency and severity of hypoglycemic episodes.

1011-P

Selecting the Initial Multiplier and Target Glucose of a Computer-Guided Algorithm (Glucommander) during Treatment of Diabetic Ketoacidosis

DAVID REYES-UMPIERREZ, FRANCISCO J. PASQUEL, RAYMIE MCFARLAND, ROBBY BOOTH, BRUCE W. BODE, GUILLERMO E. UMPIERREZ, *Atlanta, GA, Greenville, SC*

A variety of computer-based algorithms to direct the nursing staff adjusting insulin infusion rate are commercially available for the management of hyperglycemia in critically ill patients. The Glucommander (Glytec®) system estimates the rate of insulin infusion using a multiplier or insulin sensitivity factor that for most patients ranges between 0.01 and 0.03. No previous studies have determined what are the best initial multiplier and blood glucose (BG) target in diabetic ketacidosis (DKA). In this retrospective study, data from 1,750 patients with DKA treated with glucommander in 34 medical centers in the U.S. was analyzed. We evaluated the rate and time of resolution of hyperglycemia (<200 mg/dl) and metabolic acidosis (bicarbonate >18 mmol/l), and frequency of hypoglycemia (<70 mg/dl) of different multipliers ranging from 0.01 to 0.03 targeting different BG targets between 120-180 mg/dL. The admission BG was 598±255 mg/dl, bicarbonate 11±4.5 mmol/l, and pH 7.2±2.5. The time to correct hyperglycemia and metabolic acidosis was 11.3±10.6 and 21.4±27 hours, respectively. A total of 225 (13.5%) patients developed hypoglycemia during insulin infusion.

The optimal treatment outcomes were achieved with an initial multiplier of 0.01 and a glucose target range of 120-180 mg/dl; the time to correct hyperglycemia and metabolic acidosis was 9.7±8.9 and 19.6±18.7 hours, respectively. A total of 32 (7.9%) patients had hypoglycemia. There were no differences in the time to resolution of hyperglycemia or in the number of hypoglycemia using a multiplier of 0.01 or 0.02 when BG target was between 120-180 mg/dl; however, an initial multiplier of 0.03 or a lower target of 100-140 mg/dl resulted in higher rate of hypoglycemia (16.1% and 26.6%), respectively.

The results of this study indicate that when using the glucommander system, a conservative initial multiplier (0.01) and BG target of 120-180 mg/dl are safe and effective in treating patients with DKA.

Supported By: Jacobs Family Foundation

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—NON-INSULIN INJECTABLES

Moderated Poster Discussion: GLP-1 RA and Insulin—Living the Single Life or Married to the Better Half? *(Posters: 1012-P to 1019-P), see page 17.*

1012-P

The Effects of Semaglutide on β-cell Function in Subjects with Type 2 Diabetes

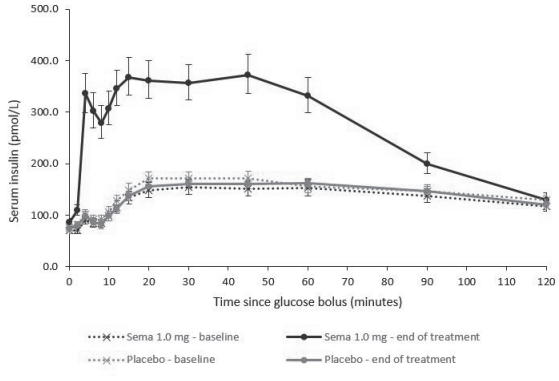
CHRISTOPH KAPITZA, KIRSTEN DAHL, JACOB BONDE JACOBSEN, MADS BUHL AXELSEN, ANNE FLINT, *Neuss, Germany, Søborg, Denmark*

Subjects with type 2 diabetes (T2D, n=75; mean HbA_{1c} 7.3%, duration of T2D 8.5 years, BMI 29.6 kg/m^2, age 56 years, 68% male) were randomized 1:1 to receive semaglutide, a once-weekly GLP-1 analog (escalated to 1.0

For author disclosure information, see page A696.

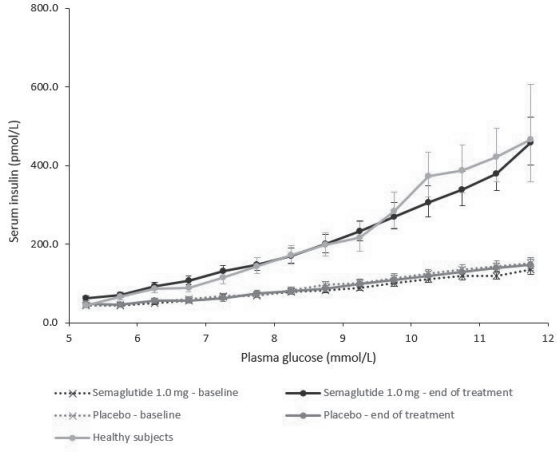
mg) or placebo for 12 weeks. Untreated healthy subjects (n=12; mean BMI 26.8 kg/m^2, age 43 years, 67% male) were included in a graded glucose infusion (GGI) test. The semaglutide:placebo ratio for change from baseline to end-of-treatment AUC following intravenous glucose tolerance (Figure 1), arginine stimulation and GGI tests (Figure 2) showed larger insulin response for semaglutide (p<0.0001). After 12 weeks, the insulin secretion rate during GGI tests showed that β-cell responsiveness in semaglutide-treated subjects with T2D was comparable to that of untreated healthy controls (Figure 2). There were no safety or tolerability issues.

Figure 1. Insulin Response to the Intravenous Glucose Tolerance Test in Subjects with T2D Receiving Semaglutide or Placebo.



After intravenous infusion with a 25 g glucose bolus, the semaglutide:placebo ratio for change from baseline to end-of-treatment in the Area Under the Curve (AUC) was larger for first-phase (0–10 min) and second-phase (10–120 min) insulin response (estimated treatment ratio: 3.02 and 2.10, respectively; p<0.0001 for both).

Figure 2. Insulin Response to a Graded Glucose Infusion in Subjects with T2D and Healthy Controls.



A continuous glucose infusion was adjusted to achieve target levels of 5, 6, 7, 8, 9, 10, 11 and 12 mmol/L over 180 min, with blood drawn for analysis throughout. Both the insulin secretion rate and slope at end of treatment for semaglutide were comparable to those of untreated healthy subjects.

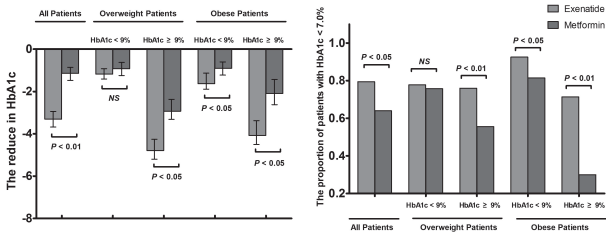
1013-P

Comparative Assessment of Therapeutic Effects of Exenatide and Metformin in Overweight/Obese Patients with Newly Diagnosed Type 2 Diabetes

JIA LIU, YANJIN HU, NING YANG, YUMEI JIA, YUAN XU, GUANG WANG, *Beijing, China*

This study assessed the therapeutic effect of exenatide and Metformin in overweight/obese patients with type 2 diabetes (T2D) under different glycemic status. A total of 230 overweight/obese patients with newly diagnosed T2D were assigned to 12 weeks of exenatide or Metformin treatment, and the changes of metabolic parameters in patients with moderate (HbA1c < 9%) or severe hyperglycemia (HbA1c ≥ 9%) were compared. In all patients, the reductions of fasting blood glucose (FBG) and HbA1c and the proportion of patients with HbA1c < 7.0% were higher in the exenatide group than the Metformin group (all $P < 0.05$). In overweight patients with moderate hyperglycemia, there was no difference in the reductions of FBG and HbA1c and the proportion of patients with HbA1c < 7.0% between exenatide and Metformin treatment. In overweight patients with severe hyperglycemia and obese patients with moderate or severe hyperglycemia, exenatide decreased FBG and HbA1c levels more significantly than Metformin, moreover, the proportion of patients with HbA1c < 7.0% was higher after exenatide treatment (all $P < 0.05$). For initial therapy in newly diagnosed T2D patients, exenatide and Metformin have similar efficacy in overweight patients with moderate hyperglycemia, however, exenatide was better than Metformin in obese patients and overweight patients with severe hyperglycemia.

Figure.



Supported By: National Natural Science Foundation of China (81270369); Beijing Natural Science Foundation (7142060); Beijing Municipal Administration of Hospitals (QML20150308)

1014-P

Effect of Exenatide Once Weekly on Glycemic Fluctuations in Patients with T2D

JUAN P. FRIAS, JAMES A. RUGGLES, SERGEY ZHUPLATOV, SAMER NAKHLE, ERIC J. KLEIN, RONG ZHOU, LEI SHI, POUL STRANGE, *Los Angeles, CA, Fort Washington, PA, Las Vegas, NV, Olympia, WA, Cincinnati, OH, Princeton Junction, NJ*

Glycemic fluctuations are an important clinical consideration when managing patients with T2D. This randomized controlled double-blind phase 4 clinical study investigated the quality of glucose control with exenatide QW (EQW) vs. placebo (PBO) using continuous glucose monitoring (CGM). Patients with T2D inadequately controlled on Metformin (MET) were randomized to EQW 2 mg or PBO for 10 wks. Glucose concentration was measured over 7 days at baseline and wks 4 and 10 using CGM (Dexcom G4). At baseline mean age, A1c, fasting plasma glucose (FPG) and 2h postprandial glucose (PPG) in the EQW (N=60)/PBO (N=56) groups were 55/56 y, 8.2%/8.0%, 178/168 mg/dL and 221/221 mg/dL, respectively. Compared with PBO (LS mean treatment difference for change from baseline), EQW significantly (P<0.001) reduced 24h mean weighted glucose (wks 4, 10: –21 mg/dL; –28 mg/dL), FPG (–28 mg/dL; –37 mg/dL), and PPG (–30 mg/dL; –38 mg/dL). There was no difference in mean weighted glucose on Day 1 and Day 6 of wk 10 with EQW (150; 151 mg/dL). EQW resulted in a significantly (P<0.001) greater reduction in mean amplitude of glucose excursions (MAGE) vs. PBO at wk 10 (–18 mg/dL). Time in the euglycemic range significantly (P<0.001) increased from baseline to wks 4 and 10 in the EQW group, through reductions in the hyperglycemic range with no increase in time in the hypoglycemic range. For EQW vs. PBO, time in euglycemic range was 53% vs. 55% at baseline, 71% vs. 60% at wk 4, and 77% vs. 58% at wk 10. Time in hyperglycemic range was 47% vs. 45%, 29% vs. 40%, and 22% vs. 42%. Time in hypoglycemic range was 0.1% vs. 0.1%, 0.6% vs. 0.3%, and 0.7% vs. 0.3%. In patients with T2D uncontrolled on MET, EQW significantly improved overall glycemic control and reduced glucose fluctuations as early as wk 4, as determined by reductions in FPG, PPG, 24h mean weighted glucose, MAGE, and time in the hyperglycemic range. Improvements in glycemic control were not accompanied by an increase in hypoglycemia and glycemic control was consistent throughout wk 10 as shown by 24h glucose.

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1015-P

Cardiovascular Effects of Liraglutide in Patients with Type 1 Diabetes

THOMAS F. DEJGAARD, NANNA B. JOHANSEN, CHRISTIAN S. FRANDSEN, ALI ASMAR, LISE TARNOW, FILIP K. KNOP, STEN MADSBAD, HENRIK U. ANDERSEN, *Gentofte, Denmark, Hvidovre, Denmark, Copenhagen, Denmark, Hillerød, Denmark, Hellerup, Denmark*

The add-on of the glucagon-like peptide-1 receptor agonist liraglutide to insulin treatment in type 1 diabetes reduces insulin requirements, frequency of hypoglycemia and bodyweight. However, the effects on cardiovascular risk factors including 24h ambulatory blood pressure (AmBP), 24h heart rate (HR) and arterial stiffness remain unknown. In a double-blind, placebo-controlled design we randomized 100 patients with type 1 diabetes, HbA1c >64 mmol/mol and BMI >25 kg/m^2 to 24 weeks of liraglutide 1.8 mg once-daily or placebo (1:1) added to preexisting basal-bolus insulin treatment. At randomiza-

tion and after 24 weeks of treatment, 24h AmBP, 24h HR and arterial stiffness (assessed by pulse wave velocity) were evaluated. Mean baseline characteristics were similar in the two groups mean age±SD: 47±13 vs. 49±12 years (liraglutide vs. placebo); HbA1c: 72±8 vs. 72±8 mmol/mol; BMI: 30.3±3.5 vs. 29.8±3.1 kg/m^2 except for diabetes duration 20±12 vs. 25±12 years. After 24 weeks, nighttime HR and diastolic blood pressure increased by 6.5 bpm (95% CI: 2.2 - 10.8, p=0.003) and 4.9 mmHg (95% CI: 0.8 - 9.0, *P*=0.020), respectively, in liraglutide-treated compared with placebo-treated patients. Changes in daytime and nighttime systolic blood pressure, daytime diastolic blood pressure and HR did not differ between groups. In a post-hoc analysis of patients with daytime systolic blood pressure above the median (136 mmHg), daytime systolic blood pressure decreased by 6.0±10.4 and 10.5±15.0 mmHg in the liraglutide and placebo group, respectively (*P*=0.490), and nighttime systolic blood pressure decreased by 4.7±13.0 and 7.0±15.9 mmHg, respectively (*P*=0.207). Changes in pulse wave velocity did not differ between groups (*P*=0.918). In overweight patients with type 1 diabetes and insufficient glycemic control, addition of 1.8 mg liraglutide increased nighttime HR and diastolic blood pressure, but did not affect daytime or nighttime systolic blood pressure, daytime diastolic blood pressure or arterial stiffness.

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1016-P

The Efficacy and Safety of Lixisenatide in Asian Patients with Type 2 Diabetes (T2D) Insufficiently Controlled with Basal Insulin +/- Metformin: The GetGoal-L-C Trial

WENYING YANG, NIANXIAN ZHANG, ELISABETH NIEMOELLER, SHUHUA SHANG, GETGOAL-L-C STUDY GROUP, *Beijing, China, Shanghai, China, Frankfurt, Germany*

Patients (n=448) with inadequately controlled T2D were randomized (1:1) to lixisenatide or placebo (PBO) as add-on to basal insulin (BI) ± Metformin (Met) after an 8-wk run-in, with BI titration to a target (SMPG of 80-100 mg/dL). Primary endpoint was change in HbA_{1c} from baseline (BL) to wk 24. 2-h PPG, 7-point SMPG, body weight, insulin dose, FPG, and adverse events (AEs) were also assessed. BL demographics were similar across arms (mean age 55 yrs; most patients Asian [86%]; mean BMI 28 kg/m^2; mean T2D duration 10 yrs). Lixisenatide was superior vs. PBO in mean change from BL to wk 24 in HbA_{1c} (Table). The percentage of responders (HbA_{1c} <7% or ≤6.5%) was greater in the lixisenatide arm vs. PBO. Significant improvements were seen for 2-h PPG, 7-point SMPG profile, weight loss, and daily BI dose in the lixisenatide arm vs. PBO (Table). The percentage of treatment-emergent AEs was higher in the lixisenatide arm vs. PBO (64% vs. 41%), mainly due to gastrointestinal events (Table). The incidence of any symptomatic hypoglycemia was low and comparable between arms (lixisenatide 16%; PBO 14%). In conclusion, in Asian patients insufficiently controlled on BI ± Met, lixisenatide was superior vs. PBO in glycemic control, along with a tolerability profile in line with the GLP-1 RA class.

Table.

Parameter	Lixisenatide (GLP-1, QD) (n=223)	Placebo (n=223)
HbA_{1c}, %		
Baseline (SD)	7.90 (0.66)	7.93 (0.69)
Wk 24 (LOCF; SD)	7.41 (1.08)	7.94 (1.01)
LS change from baseline at Wk 24 (SE)	–0.62 (0.09)	–0.11 (0.09)
LS mean (SE) difference vs placebo	–0.51 (0.09)	–
P-value	<0.0001	–
HbA_{1c} response, n (%)		
≤6.5%	49 (22.3)	13 (5.9)
<7%	82 (37.3)	30 (13.6)
P-value (for <7%)	<0.0001	–
2-h PPG, mg/dL		
Baseline (SD)	246.78	253.26 (65.16)
Wk 24 (LOCF; SD)	192.06 (89.10)	257.22 (73.80)
LS change from baseline at Wk 24 (SE)	–73.08 (7.34)	–10.98 (7.47)
LS mean (SE) difference vs placebo	–62.10 (7.13)	–
P-value	<0.0001	–
Average 7-point SMPG, mg/dL		
Baseline (SD)	165.96 (33.66)	167.4 (33.48)
Wk 24 (LOCF; SD)	160.20 (32.76)	170.46 (34.92)
LS change from baseline at Wk 24 (SE)	–8.64 (3.08)	1.08 (3.10)
LS mean (SE) difference vs placebo	–9.72 (3.02)	–
P-value	0.0014	–
Body weight, kg		
Baseline (SD)	74.19 (14.05)	74.59 (13.29)
Wk 24 (LOCF; SD)	73.06 (13.81)	74. 64 (13.29)
LS change from baseline at Wk 24 (SE)	–1.24 (0.22)	–0.07 (0.22)
LS mean (SE) difference vs placebo	–1.17 (0.22)	–
P-value	<0.0001	–
Total daily insulin dose, U		
Baseline (SD)	39.85 (19.15)	37.51 (16.07)
Wk 24 (LOCF; SD)	37.77 (18.74)	36.78 (16.02)
LS change from baseline at Wk 24 (SE)	–2.98 (0.39)	–1.87 (0.39)
LS mean (SE) difference vs placebo	–1.11 (0.38)	–
P-value	0.0033	–
FPG, mg/dL		
Baseline (SD)	126.90 (37.08)	124.56 (32.22)
Wk 24 (LOCF; SD)	130.68 (40.14)	136.98 (43.56)
LS change from baseline at Wk 24 (SE)	3.06 (3.69)	9.90 (3.798)
LS mean (SE) difference vs placebo	–6.84 (3.71)	–
P-value	0.0650	–
TEAEs, n (%)*	143 (63.8)	91 (40.8)
Nausea and vomiting, n (%)*	62 (27.7)	12 (5.4)
Hypoglycemia, n (%)*,†		
Blood glucose <60 mg/dL	20 (8.9)	20 (9.0)

Data are means unless stated otherwise. Background therapy was basal insulin ± metformin
*Lixisenatide n=224; placebo n=223; †Number of patients with events
FPG=fasting plasma glucose; HbA_{1c}=glycosylated hemoglobin; LOCF=last observation carried forward; LS=least squares; 2-h PPG=2-h postprandial plasma glucose; SD=standard deviation; SE=standard error; SMPG=self-monitored plasma glucose; TEAE=treatment emergent adverse event

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1017-P

Consistent Outcomes across Dose Ranges with Titratable LixiLan, Insulin Glargine/Lixisenatide Fixed-Ratio Combination, in the LixiLan-O Trial

ROBERT R. HENRY, BO AHRÉN, MELANIE DAVIES, YUJUN WU, YEHUDA HANDELSMAN, ELISABETH SOUHAMI, ELISABETH NIEMOELLER, JULIO ROSENSTOCK, LIXILAN-O TRIAL INVESTIGATORS, *San Diego, CA, Lund, Sweden, Leicester, United Kingdom, Bridgewater, NJ, Tarzana, CA, Paris, France, Frankfurt, Germany, Dallas, TX*

Efficacy and safety of LixiLan, a novel titratable fixed-ratio combination of insulin glargine (Gla-100) with lixisenatide, was compared with Gla-100 alone and lixisenatide alone in T2DM inadequately controlled on Metformin (MET) ± a second oral glucose-lowering drug. Participants (n=1170) were randomized (2:2:1) to once-daily LixiLan, Gla-100 (max 60 U/day), or lixisenatide (20 µg maintenance dose) plus MET for 30 wks. LixiLan provided statistically superior glycemic control compared with Gla-100 and lixisenatide alone. In this exploratory analysis, efficacy and safety were evaluated for LixiLan based on Gla-100 and lixisenatide doses at study end. Reduction in HbA_{1c} and percentages achieving HbA_{1c} <7% with LixiLan were consistent across Gla-100 and lixisenatide dose categories at wk 30. Across all LixiLan doses, the body weight increase seen with insulin alone was mitigated. With LixiLan, incidence of documented symptomatic hypoglycemia (BG ≤70 mg/dL) was similar across final dose categories of insulin and lixisenatide (Table). Incidence of nausea/vomiting was low (Table), related to the slow titration of lixisenatide in the combination. In conclusion, LixiLan efficacy and safety, with a low frequency of nausea and vomiting, was consistent across all final dose categories of its Gla-100 and lixisenatide components.

Table.

	LixiLan (fixed-ratio combination, QD)			Gla-100 (insulin glargine, QD)		
	HbA_{1c}, %	HbA_{1c} <7%, n (%)	Body weight (kg)	HbA_{1c}, %	HbA_{1c} <7%, n (%)	Body weight (kg)
Final Gla-100 dose						
≥10 – <20 U (n)	57		57	38		38
Baseline	7.8		79.1	7.8		80.9
Week 30	6.4	40 (69)	–	6.7	20 (51)	–
LS mean change ± SE	–1.44 ± 0.10		–1.8 ± 0.50	–1.29 ± 0.122		–0.9
95% CI	–1.65, –1.24	57.06, 80.87	–2.75, –0.78	–1.53, –1.06	35.59, 66.97	–2.16, 0.37
≥20 – 30 U (n)	76		76	95		96
Baseline	7.9		83.4	8.0		82.9
Week 30	6.4	55 (72)	–	6.8	55 (57)	–
LS mean change ± SE	–1.58 ± 0.09		–1.5 ± 0.42	–1.29 ± 0.07		0.8 ± 0.40
95% CI	–1.75, –1.41	62.31, 82.42	–2.38, –0.71	–1.44, –1.15	47.40, 67.19	–0.04, 1.54
≥30 – ≤40 U (n)	126		126	117		117
Baseline	8.1		87.7	8.1		87.3
Week 30	6.4	100 (79)	–	6.6	85 (73)	–
LS mean change ± SE	–1.68 ± 0.07		–0.5 ± 0.32	–1.46 ± 0.07		1.0 ± 0.35
95% CI	–1.81, –1.55	72.30, 86.43	–1.10, 0.18	–1.59, –1.33	64.57, 80.73	0.29, 1.68
<40 – ≤60 U (n)	208		208	209		209
Baseline	8.2		95.5	8.2		96.0
Week 30	6.6	150 (72)	–	7.0	115 (55)	–
LS mean change ± SE	–1.5 ± 0.05		0.60 ± 0.26	–1.12 ± 0.05		1.94 ± 0.27
95% CI	–1.60, –1.40	66.02, 78.21	0.09, 1.10	–1.22, –1.02	48.28, 61.77	1.40, 2.47
Final lixisenatide dose						
≥5 – <10 µg (n)	57		57			
Baseline	7.8		79.1			
Week 30	6.4	40 (69)	–			
LS mean change ± SE	–1.44 ± 0.10		–1.71 ± 0.50			
95% CI	–1.64, –1.24	57.06, 80.87	–2.70, –0.72			
≥10 – <15 µg (n)	131		131			
Baseline	8.0		85.7			
Week 30	6.4	101 (77)	–			
LS mean change ± SE	–1.63 ± 0.07		–1.07 ± 0.32			
95% CI	–1.76, 1.51	69.90, 84.29	–1.70, –0.44			
≥15 – ≤20 µg (n)	275		275			
Baseline	8.2		93.3			
Week 30	6.6	200 (73)	–			
LS mean change ± SE	–1.54 ± 0.04		0.34 ± 0.22			
95% CI	–1.63, –1.45	67.46, 77.99	–0.09, 0.78			

Adverse events	Documented symptomatic hypoglycemia*	Nausea	Documented symptomatic hypoglycemia	Nausea
Final Gla-100 dose				
<30 U				
n (%)	35 (26)	16 (12)	42 (30)	3 (2)
Events/patient year	2.0	0.4	2.0	0.04
≥30 U				
n (%)	85 (25)	29 (9)	68 (21)	14 (4)
Events/patient years	1.2	0.2	0.9	0.07
Final lixisenatide dose				
<10 µg				
n (%)	13 (22)	4 (7)		
Events/patient year	1.7	0.2		
≥10 – <15 µg				
n (%)	41 (31)	17 (13)		
Events/patient year	1.8	0.4		
≥15 – 20 µg				
n (%)	66 (24)	24 (9)		
Events/patient year	1.3	0.2		

Gla-100=insulin glargine; HbA_{1c}=glycated hemoglobin; LixiLan=fixed-ratio combination of Gla-100 and lixisenatide; U=units
*Documented symptomatic hypoglycemia was defined as ≤70 mg/dL
LS mean change was calculated only for categories with ≥5 patients; groups with <5 patients not shown

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1018-P

Efficacy and Safety of LixiLan vs. Insulin Glargine According to Baseline Characteristics in Patients with Type 2 Diabetes from the LixiLan-L Trial

CAROL WYSHAM, RICCARDO C. BONADONNA, VANITA ARODA, MANUEL PUIG DOMINGO, CHRISTOPH KAPITZA, WILLIAM STAGER, CHRISTINE YU, ELISABETH NIEMOELLER, ELISABETH SOUHAMI, RICHARD BERGENSTAL, LIXILAN-L TRIAL INVESTIGATORS, *Spokane, WA, Parma, Italy, Hyattsville, MD, Barcelona, Spain, Neuss, Germany, Bridgewater, NJ, Frankfurt, Germany, Paris, France, Portland, OR*

The LixiLan-L open-label trial compared the efficacy and safety of LixiLan, a novel fixed-ratio combination of insulin glargine (Gla-100) and lixisenatide, with Gla-100 over 30 weeks in patients with type 2 diabetes (T2D) inadequately controlled on basal insulin (± ≤2 oral antidiabetic drugs). In this analysis, safety and efficacy outcomes were assessed within subgroups according to baseline characteristics ([BC]; glycated hemoglobin [HbA_{1c}] <8, ≥8%; body mass index <30, ≥30 kg/m^2; duration of T2D <10, ≥10 years). Reduction in HbA_{1c}, proportion of responders achieving HbA_{1c} <7%, and incidence of hypoglycemia (≤70 mg/dL) for the BC subgroups are shown (Table). There were no major changes in parameters across subgroups and efficacy was maintained in patients with high HbA_{1c}. The LixiLan treatment group showed consistently greater glycemic control and more responders compared with the Gla-100 group in all of the subpopulations tested. Hypoglycemia varied slightly for subgroups (Table), without marked differences observed. In conclusion, LixiLan consistently improved glycemic control compared with Gla-100 in all subgroups of BC, including the most challenging groups of patients with long duration of diabetes, obesity, and high HbA_{1c}.

Table.

Baseline characteristics subgroup (N=LixiLan/Gla-100)	Parameters	LixiLan (fixed-ratio combination, QD)			Gla-100 (insulin glargine, QD)		
		HbA_{1c}, %	%HbA_{1c}<7%*	Hypo, %† (e/p-y)	HbA_{1c}, %	%HbA_{1c}<7%*	Hypo, %† (e/p-y)
HbA_{1c} <8% (N=165/163) for Resp (N=166/163) for Hypo (N=54/69)	BL	7.5	67.5	32.7 (2.0)	7.4	45.4	42.3 (3.4)
	Week 30	6.7			7.1		
	Change	−0.8			−0.3		
	‡Diff				−0.5±0.1	22.8±5.2	
HbA_{1c} ≥8% (N=199/201) for Resp (N=200/202) for Hypo (N=92/86)	BL	8.6	44.5	46.0 (3.9)	8.6	16.8	42.6 (4.9)
	Week 30	7.2			7.8		
	Change	−1.4			−0.8		
	‡Diff				−0.5±0.1	27.7±4.3	
Duration of diabetes <10 years (N=166/150) for Resp (N=168/150) for Hypo (N=166/150)	BL	8.0	56.0	41.0 (2.8)	8.0	35.3	36.7 (3.0)
	Week 30	6.9			7.4		
	Change	−1.1			−0.6		
	‡Diff				−0.5±0.1	20.8±5.2	
Duration of diabetes ≥10 years (N=198/213) for Resp (N=199/214) for Hypo (N=199/214)	BL	8.1	54.3	39.2 (3.3)	8.1	25.7	46.7 (5.1)
	Week 30	7.0			7.6		
	Change	−1.1			−0.6		
	‡Diff				−0.5±0.1	28.6±4.4	
BMI <30 kg/m^2 (N=155/156) for Resp (N=156/156) for Hypo (N=74/78)	BL	8.1	58.3	47.7 (4.8)	8.1	27.6	50.0 (6.3)
	Week 30	7.0			7.6		
	Change	−1.1			−0.5		
	‡Diff				−0.6±0.1	31.4±5.0	
BMI ≥30 kg/m^2 (N=209/208) for Resp (N=210/209) for Hypo (N=72/77)	BL	8.1	52.4	34.3 (1.8)	8.1	31.1	36.8 (2.7)
	Week 30	7.0			7.4		
	Change	−1.1			−0.6		
	‡Diff				−0.5±0.1	21.1±4.5	

All data are mean unless stated otherwise
*Responders are defined as patients who achieved HbA_{1c} <7% at Week 30
†Incidence of documented symptomatic hypoglycemia (% of patients experiencing hypoglycemia, where hypoglycemia is defined as an event with typical symptoms accompanied by a measured plasma glucose concentration of ≤70 mg/dL [≤3.9 mmol/L])
‡Diff=mean difference LixiLan vs Gla-100±SE, SE using ANOVA or CMH estimates
BL=baseline; BMI=body mass index; e/p-y=event per patient-year; HbA_{1c}=glycated hemoglobin; Hypo=hypoglycemia; Resp=responders; SE=standard error

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1019-P

Safe and Effective Lowering of Blood Glucose with Insulin Degludec/Liraglutide (IDegLira) in Elderly Patients with Type 2 Diabetes Uncontrolled on Oral Antidiabetic Drugs and/or Insulin Glargine (IGlar)

ILDIKO LINGVAY, CHRISTOPHER H. SORLI, SULTAN LINJAWI, TRINE J. ABRAHAMSEN, LUCINE LEHMANN, ANDREAS LIEBL, *Dallas, TX, Billings, MT, Coffs Harbour, Australia, Søborg, Denmark, Bad Heilbrunn, Germany*

This analysis investigated the safety and efficacy of IDegLira in elderly (≥65 years) patients uncontrolled on Metformin ± pioglitazone (DUAL I) or IGlar (DUAL V). The DUAL I and DUAL V 26 week trials demonstrated the clinical benefits of IDegLira vs. IDeg or Lira alone and vs. continued IGlar uptitration in the entire trial populations.

In DUAL I and DUAL V respectively, 14% and 26% of patients were ≥65 years old (median: 69.6 and 69.8 years; body weight: 82.1 and 84.3 kg). A1c reduction was significantly greater for IDegLira vs. comparators with more patients achieving A1c <7% (Table). FPG reduction was similar for IDegLira vs. insulin comparators of both trials but significantly greater for IDegLira vs. Lira in DUAL I. IDegLira was associated with weight loss vs. weight gain with both IDeg and IGlar, but less weight loss than Lira (statistically significant difference for all). Confirmed hypoglycemia rates were similar vs. IDeg in DUAL I and significantly lower vs. IGlar in DUAL V. IDegLira was insulin-sparing vs. both insulin comparators. Safety profiles were consistent with the entire trial populations.

In elderly patients IDegLira led to better glycemic control vs. glucagon-like peptide-1 analogue and basal insulin, the advantage of weight loss compared with insulin alone, and low rates of hypoglycemia.

Table.

		Change in A1C from baseline, %	Change in FPG from baseline, mg/dL	Change in weight from baseline, kg	Confirmed hypoglycaemia	Daily insulin dose at end of trial, U	Patients with A1C <7%, %
DUAL I	Observed data	Mean (SD)	Mean (SD)	Mean (SD)	Episodes/100 PYE	Mean (SD)	Proportion
	IDegLira (N=118)	-1.89 (1.06)	-69.5 (48.8)	-0.5 (3.1)	223.2	33 (13)	90.7
	IDeg (N=61)	-1.37 (0.89)	-68.9 (50.0)	2.1 (3.5)	246.6	44 (27)	75.4
	Lira (N=57)	-1.33 (0.95)	-27.5 (39.5)	-3.2 (3.6)	15.3	NA	66.7
	Estimate [95% CI], *p* IDegLira vs. IDeg	ETD: -0.54 [-0.80; -0.28], *p*<0.0001	ETD: -1.48 [-10.51; 7.55], NS	ETD: -2.59 [-3.65;-1.53], *p*<0.0001	ERR: 0.83 [0.48; 1.46], NS	ETD: -11 [-17; -5], *p*=0.0002	EOR: 3.29 [1.28; 8.46], *p*=0.0135
	Estimate [95% CI], *p* IDegLira vs. Lira	ETD: -0.66 [-0.93; -0.39], *p*<0.0001	ETD: -36.6 [-45.98; -27.22], *p*<0.0001	ETD: 2.54 [1.44; 3.65], *p*<0.0001	ERR: 18.10 [5.04; 65.02], *p*<0.0001	NA	EOR: 6.48 [2.53; 16.61], *p*<0.0001
DUAL V	Observed data	Mean (SD)	Mean (SD)	Mean (SD)	Episodes/100 PYE	Mean (SD)	Proportion
	IDegLira (N=68)	-1.75 (1.03)	-40.5 (47.8)	-1.9 (2.7)	106.1	37 (11)	70.6
	IGlar (N=77)	-0.89 (0.82)	-45.9 (43.8)	1.3 (3.1)	400.5	54 (24)	37.7
	Estimate [95% CI], *p* IDegLira vs. IGlar	ETD: -0.71 [-0.95; -0.48], *p*<0.001	ETD: 2.08 [-7.71; 11.86], NS	ETD: -3.07 [-4.01; -2.13], *p*<0.001	ERR: 0.26 [0.14; 0.48], *p*<0.001	ETD: -17.05 [-23.12; -10.97] *p*<0.001	EOR: 5.52 [2.52; 12.10], *p*<0.001

Data based on the full analysis set, with the exception of the observed rates of confirmed hypoglycemia and insulin dose at end of trial, which are based on the safety analysis set. Missing data imputed using last observation carried forward. Confirmed hypoglycemia was defined as severe or plasma glucose <56 mg/dL. Change from baseline in HbA_{1c}, FPG, body weight and insulin dose are analyzed using an ANCOVA model, the number of confirmed hypoglycemic episodes are analyzed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset, while the responder endpoints are analyzed using a logistic regression model with a logit link. ANCOVA, analysis of covariance; EOR; estimated odds ratio; ETD, estimated treatment difference; ERR, estimated rate ratio; FPG, fasting plasma glucose; IDeg, insulin degludec; Lira, liraglutide; N, number of patients; NA, not applicable; NS, not significant; PYE, patient-years of exposure; SD. standard deviation.

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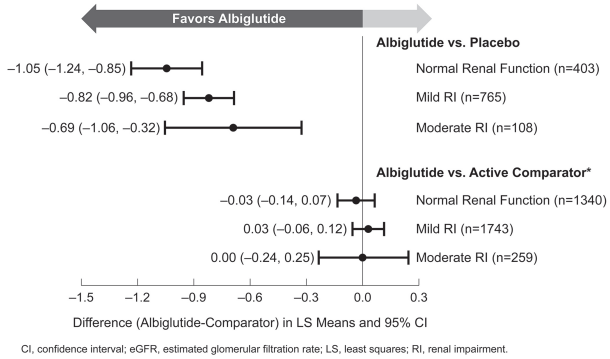
1020-P

Effects of Mild to Moderate Renal Impairment on Albiglutide (ALBI) in Type 2 Diabetes (T2DM)

LAWRENCE A. LEITER, ANGELA JONES-LEONE, ANDRE ACUSTA, VERONICA BAINBRIDGE, BO AHRÉN, *Toronto, ON, Canada, Philadelphia, PA, Collegeville, PA, Guildford, United Kingdom, Lund, Sweden*

Renal impairment (RI) is a frequent comorbidity in T2DM. In the HARMONY Phase 3 trials of patients with T2DM, treatment with the glucagon-like peptide-1 receptor agonist ALBI resulted in HbA_{1c} reduction, fasting plasma glucose reduction, and weight loss compared with agents associated with weight gain (funded by GSK). ALBI was generally well tolerated. Here we present post-hoc pooled analyses of the relationship between renal function and least square mean change in HbA_{1c} (from baseline to end-of-trial) in HARMONY 1-7. These trials of ALBI 30-50 mg/week had placebo and/or active antihyperglycemic controls, ranged from 26 to 104 weeks in length, and prescribed different concomitant medications. Patients at baseline were ≥18 years old with HbA_{1c} 7.0-10.5% and estimated creatinine clearance >60 mL/min. ALBI reduced HbA_{1c} significantly more than placebo across subgroups based on renal function and was noninferior to active comparators in HbA_{1c} reduction. The relationship between ALBI and active comparators was not affected by renal function (Figure). In addition, there was no overall worsening of renal function (estimated glomerular filtration rate) with ALBI vs. pooled comparators. These results are consistent with efficacy of ALBI in T2DM patients with mild to moderate RI, with no dose adjustment required.

Figure. Difference (Albiglutide-comparator in LS Mean Change from Baseline in HbA_{1c} by Renal Function.



CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares; RI, renal impairment.
Normal (eGFR ≥90 mL/min/1.73 m^2); Mild RI (60 ≤eGFR <90 mL/min/1.73 m^2); Moderate RI (30 ≤eGFR <60 mL/min/1.73 m^2).
*Active comparators: insulin glargine, insulin lispro, glimepiride, liraglutide, pioglitazone, or sitagliptin.

1021-P

Effect on Cardiac Function of Exercise Combined with Glucagon-like Peptide-1 Receptor Agonist Treatment: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

PETER G. JØRGENSEN, MAGNUS T. JENSEN, PERNILLE MENSBERG, HEIDI STORGAARD, SIGNE NYBY, JAN S. JENSEN, BENTE KIENS, ERIK A. RICHTER, FILIP K. KNOP, TINA VILSBØLL, *Hellerup, Denmark, Nærum, Denmark, Copenhagen, Denmark*

In patients with type 2 diabetes, supervised exercise improves cardiac function. We evaluated the effect of supervised exercise combined with glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment on cardiac function in sedentary patients with type 2 diabetes. Thirty-three dysregulated (HbA_{1c}: 65±14 mmol/mol), and overweight (body mass index: 32±4 kg/m^2) patients with type 2 diabetes on diet and/or Metformin treatment were randomly assigned to exercise (3 supervised 60-minute training sessions per week) in addition to either liraglutide (1.8 mg once-daily) or placebo for 16 weeks. All underwent echocardiography with color tissue Doppler and 2D speckle tracking. Measures of left ventricular (LV) diastolic function (assessed as early diastolic myocardial velocity (e') were improved in the placebo group (-7.1±1.6 (mean±SD) to -7.7±1.8 cm/s, *P*=0.01), but not in the liraglutide group (-7.1±1.4 to -7.0±1.4 cm/s, *P*=0.60; between groups: *P*=0.02). Similarly, the ratio of early and atrial LV inflow velocities (e'/a') improved in the placebo group (1.0±0.4 to 1.2±0.4, *P*=0.003), but not in the liraglutide group (1.0±0.3 to 1.0±0.3, *P*=0.87; between groups: *P*=0.03). No changes in heart rate were observed in any of the groups (placebo: 70±12 to 69±13 bpm, *P*=0.50; liraglutide: 70±9 to 71±9 bpm, *P*=0.82; between groups: *P*=0.32). We found no significant differences in LV structure including wall diameters, internal dimension and mass within or between the placebo and the liraglutide groups. LV systolic function, ejection fraction and global longitudinal strain, were also similar within and between the two groups. In conclusion, addition of the GLP-1RA liraglutide to exercise in sedentary patients with dysregulated type 2 diabetes apparently seems to blunt the beneficial effect of exercise on LV diastolic function. Further research is needed to ascertain these findings and illuminate their clinical implications.

Supported By: Novo Nordisk A/S

1022-P

Weekly GLP-1 Agonist Albiglutide Monotherapy Improves Glycemic Parameters in Japanese Type 2 Diabetes Mellitus (T2DM) Patients

ANTONIO NINO, INAHA OKUDA, TIMOTHY H. WILSON, LIN YUE, HIROMU NAKAJIMA, MAHO TSUBOI, MOLLY C. CARR, *Collegeville, PA, Tokyo, Japan, Research Triangle Park, NC*

Albiglutide (Eperzan and Tanzeum; ALBI) is a GLP-1 mimetic generated by fusion of a dipeptidyl peptidase-4-resistant GLP-1 dimer to human serum albumin for the treatment of type 2 diabetes mellitus. This Phase 3, 24-week, randomized, double-blind, placebo-controlled study, with an extension to 1 year, assessed the efficacy and safety of 2 doses of ALBI monotherapy in Japanese patients with T2DM. Double-blind treatment arms included weekly ALBI 30 mg (n=160), ALBI 50 mg (n=150), and placebo (PBO, switch to ALBI 30 mg after 24 weeks, n=77). An open-label arm of daily liraglutide (Victoza; LIRA) 0.9 mg (n=103) was included for reference (with no statistical analysis). The primary analysis, comparing ALBI to PBO, was least squares adjusted mean change from baseline (CFB) in HbA_{1c} at 24 weeks: –1.08%, –1.32%, and 0.24% for ALBI 30 mg, 50 mg, and PBO, respectively (*P* vs. PBO <0.0001 for both ALBI doses). LIRA 0.9 mg daily achieved –1.19% in CFB HbA_{1c} at 24 weeks. The decreases in HbA_{1c} for both doses of ALBI were sustained over the duration of the study. Fasting plasma glucose also decreased in all active treatment groups. Mean change in body weight through 1 year was less than 1 kg across groups. The most commonly reported adverse events (AEs) were nasopharyngitis, constipation, and nausea. Incidence of AEs over 1 year was higher in active treatment groups than PBO. Serious AEs were reported in ALBI 30 mg (5/160; 3.1%) and ALBI 50 mg (6/150; 4.0%) arms. Patient withdrawal due to an AE ranged from 0% in the LIRA group to 5.3% in the ALBI 50-mg group. Few hypoglycemia events were reported across the groups, and no patient withdrew due to hypoglycemia. Antidrug antibody was reported in 8.8% of ALBI groups, but no neutralizing antibody was detected. No new safety concerns other than those in the labeling outside Japan were detected. In conclusion, ALBI monotherapy achieved clinically significant decreases in HbA_{1c} with good tolerability in Japanese patients. (NCT01733758).

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1023-P

Quantifying and Predicting Mean A1c Reductions for Exenatide QW and BID: Importance of Baseline A1c and Other Patient Characteristics

GUNTRAM SCHERNTHANER, BAPTIST GALLWITZ, JENNY HAN, ELISE HARDY, JONATHAN E. SHAW, *Vienna, Austria, Tübingen, Germany, San Diego, CA, Gaithersburg, MD, Melbourne, Australia*

There is considerable variation between individuals in regard to the A1c response to therapy. We aimed to quantify and predict responses to exenatide once weekly (ExQW) and twice daily (ExBID). Data were pooled from trials which had a duration ≥24 weeks and included self-monitored blood glucose profiles (ExQW, N=941 from 5 trials; ExBID, N=1414 from 8 trials). Patients were divided into higher, average, and lower A1c responders at 6 months, based upon tertiles of linear regression residuals that were corrected for individual participants' baseline (BL) A1c. Putative predictive BL variables were summarized by tertile. Most patients responded to ExQW or BID. Despite the markedly different A1c changes in the tertile determination, BL A1c levels were similar among the tertiles (Table). Most variables did not differ by tertile of response, and most differences between the first and third tertiles were minor (Table). Individual BL characteristics of higher responders to ExBID were Asian ethnicity, and lower fasting and higher post-breakfast glucose. Higher response to ExQW was seen in patients on diet/exercise or Metformin alone. In conclusion, we identified different predictors of response to ExQW and ExBID, which may be related to continuous vs. intermittent exposure to exenatide.

Table. Baseline Characteristics According to A1c Response Tertile for Exenatide QW and BID.

Characteristic	Exenatide QW			Exenatide BID		
A1c Response Tertile	1	3	Difference[a]	1	3	Difference[a]
A1c change from BL at Week 24 (%), mean (95% CI)	–2.51 (–2.61, –2.41)	–0.56 (–0.66, –0.45)		–1.92 (–1.98, –1.86)	–0.23 (–0.29, –0.17)	
Categorical Variables at BL (% of pp)						
Asian Race	39.4	48.7	–9.3	16.5	6.8	+9.7
Hispanic[b,c]	12.8	6.1	+6.7	5.5	4.9	+0.6
Diet/exercise only[c]	27.6	16.6	+11.0	5.3	6.8	–1.5
Metformin only	42.3	32.8	+9.5	37.3	42.4	–5.1
Dual therapy	25.3	44.9	–19.6	47.7	44.2	+3.5
Triple therapy[b, c]	1.6	1.3	+0.3	7.0	5.1	+1.9
eGFR ≥90 mL/min	37.2	46.8	–9.6	45.8	49.5	–3.7
Continuous Variables at BL (mean)						
Age (y)	54.9	54.1	+0.8	58.2	55.2	+3.0
Baseline A1c (%)	8.7	8.6	+0.1	8.1	8.1	0
Fasting glucose (mg/dL)	173.0	178.6	–5.5	170.3	184.5	–14.2
Post-breakfast glucose excursion (mg/dL)	55.9	59.3	–3.4	51.0	40.2	+10.8

BL, baseline; CI, confidence interval; pp, patient population; [a] difference between tertile 1 and 3; [b] n<100 for ExQW; [c] n<100 for ExBID.

Supported By: AstraZeneca

1024-P

Efficacy and Safety across the Final Dose Ranges in Patients with T2DM Receiving Insulin Glargine/Lixisenatide Fixed-Ratio Combination in the LixiLan-L Trial

ROBERT RITZEL, JOSEP VIDAL, VANITA R. ARODA, YUJUN WU, ELISABETH SOUHAMI, ELISABETH NIEMOELLER, ROBERT R. HENRY, LIXILAN-L TRIAL INVESTIGATORS, *Munich, Germany, Barcelona, Spain, Hyattsville, MD, Bridgewater, NJ, Paris, France, Frankfurt, Germany, San Diego, CA*

In the 30-week LixiLan-L trial, LixiLan, a novel titratable fixed-ratio combination of insulin glargine (Gla-100) and GLP-1RA lixisenatide, showed superior glycemic control over Gla-100 alone, both optimized to FPG 80-100 mg/dL (maximum 60 U/day), in patients with T2DM inadequately controlled on basal insulin ± ≤2 oral drugs. In this post hoc analysis, safety and efficacy of LixiLan were evaluated in final dose categories of Gla-100 (both groups) and lixisenatide (LixiLan group). At week 30 (study end), reductions in HbA_{1c} and proportions of responders achieving HbA_{1c} <7% were similar across dose categories. Across all dose levels, LixiLan induced body weight loss or prevented weight gain. Incidence of documented symptomatic hypoglycemia (SMPG ≤70 mg/dL) was numerically higher in patients receiving final Gla-100 dose <30 U vs. those receiving ≥30 U. This is also shown by final lixisenatide dose level. Incidence of nausea was low in the LixiLan group (Table), potentially due to slow increase of lixisenatide com-

For author disclosure information, see page A696.

ponent in the combination. Efficacy and safety of LixiLan were generally consistent across final dose categories of its Gla-100 and lixisenatide components and consistent with overall treatment groups. These results support clinically based dose titration of a fixed-ratio combination of insulin glargine and lixisenatide.

Table.

	LixiLan (fixed-ratio combination, QD)			Gla-100 (insulin glargine, QD)		
	HbA_{1c}, %	HbA_{1c} <7%, n/N (%)	Body weight (kg)	HbA_{1c}, %	HbA_{1c} <7%, n/N (%)	Body weight (kg)
Final Gla-100 dose						
≥10 – <20 U (n)	2		2	3		3
Baseline	8.2		73	8.1		82.0
Week 30	7.3	1/2 (50)		7.4	2/3 (67)	
LS mean change (SE)						
≥20 – <30 U (n)	43		44	39		39
Baseline	8.1		77.5	7.7		78.9
Week 30	7.3	22/44 (50)		7.4	14/39 (36)	
LS mean change (SE)	–0.81 (0.124)		–1.40 (0.495)	–0.54 (0.133)		–0.29 (0.435)
95% CI	–1.06, –0.57		–2.38, –0.43	–0.80, –0.28		–1.15, 0.56
≥30 – <40 U (n)	96		96	87		87
Baseline	8.0		83.9	8.1		83.9
Week 30	6.9	47/97 (49)		7.5	28/87 (32)	
LS mean change (SE)	–1.13 (0.086)		–1.69 (0.333)	–0.60 (0.088)		0.57 (0.285)
95% CI	–1.30, –0.96		–2.35, –1.04	–0.78, –0.43		0.01, 1.31
≥40 – ≤60 U (n)	222		222	235		236
Baseline	8.1		91.7	8.1		89.7
Week 30	6.9	131/222 (59)		7.5	64/236 (27)	
LS mean change (SE)	–1.17 (0.054)		0.16 (0.215)	–0.59 (0.053)		1.18 (0.173)
95% CI	–1.27, –1.06		–0.26, 0.58	–0.70, –0.49		0.84, 1.52
Final lixisenatide dose						
≥5 – <10 µg (n)	3		3			
Baseline	8.3		79.9			
Week 30	7.2	2/3 (67)				
LS mean change (SE)						
95% CI						
≥10 – <15 µg (n)	107		108			
Baseline	8.1		82.4			
Week 30	7.0	57/108 (53)				
LS mean change (SE)	–1.04 (0.081)		–1.38 (0.318)			
95% CI	–1.20, –0.88		–2.00, –0.75			
≥15 – ≤20 µg (n)	250		250			
Baseline	8.1		90.3			
Week 30	6.9	139/251 (55)				
LS mean change (SE)	–1.13 (0.051)		–0.12 (0.202)			
95% CI	–1.24, –1.03		–0.51, 0.28			

Safety				
	Documented symptomatic hypoglycemia	Nausea	Documented symptomatic hypoglycemia	Nausea
Final Gla-100 dose				
<30 U				
n (%)	22 (48)	4 (9)	21 (50)	1 (2)
Events/patient year	4.9	0.2	8.1	0.09
≥30 U				
n (%)	124 (39)	34 (11)	134 (42)	1 (0.3)
Events/patient year	2.8	0.2	3.7	0.01
Final lixisenatide dose				
<10 µg				
n (%)	1 (33)	1 (33)		
Events/patient year	1.1	0.6		
≥10 – <15 µg				
n (%)	55 (51)	16 (15)		
Events/patient year	5.3	0.4		
≥15 – 20 µg				
n (%)	88 (35)	21 (8)		
Events/patient year	2.2	0.2		

Gla-100=insulin glargine; HbA_{1c}=glycated hemoglobin; LixiLan=fixed-ratio combination of Gla-100 and lixisenatide; LS=least-squares; SE=standard error; U=units
LS mean change was calculated only for categories with ≥5 patients; groups with <5 patients are not shown

Supported By: Sanofi

1025-P

WITHDRAWN

1026-P

Potent Cholesterol Lowering Effect of the Novel Long-Acting GLP-1/Glucagon Dual Agonist (HM12525A)

SUNG YOUB JUNG, YOUNG JIN PARK, JONG SUK LEE, EUN JUNG KIM, YOUNG MI LEE, YOUNG HOON KIM, MICHAEL TRAUTMANN, SE-CHANG KWON, *Seoul, Republic of Korea, Chula Vista, CA*

HM12525A is a novel long-acting GLP-1/glucagon dual agonist for once-weekly administration. Previous studies have demonstrated that HM12525A induced greater weight loss than GLP-1 receptor agonists, and had therapeutic potentials in NASH animal models. In the present study, we evaluated the anti-hyperlipidemic effects of HM12525A, and investigated underlying mechanisms of action (MoA). First, we investigated the cholesterol lowering efficacy in a pair feeding study using fructose-fed hamsters as a hyperlipidemic model. HM12525A lowered serum cholesterol levels, especially LDL, independent of weight loss and beyond liraglutide (Victoza). In addition to lowering LDL, HM12525A increased HDL levels. To investigate the responsible MoA, we evaluated the effect of HM12525A at molecular level using in vivo and in vitro systems. In primary rat hepatocytes, HM12525A induced the expression of PPAR-α and CPT-1 through glucagon action suggesting inhibition of VLDL biogenesis by increase of hepatic β-oxidation. The chronic HM12525A treatment inhibited the action of hepatic HMG-CoA reductase, a rate-limiting enzyme for cholesterol bio-synthesis, and increased hepatic LDL receptor expression while decreasing serum levels of PCSK9 (Proprotein convertase subtilisin/kexin type 9), a known negative regulator of the LDL receptor, in normal mice and fructose-fed hamsters. In addition, HM12525A increased the hepatic expression of apolipoprotein A1 (ApoA1), a main component of HDL in hamsters. These results suggested that HM12525A exerted its potent cholesterol lowering effect via inhibition of hepatic cholesterol and VLDL bio-synthesis, and promoting the hepatic LDLR-mediated lipoprotein clearance. We hypothesize that by increasing HDL cholesterol HM12525A could have beneficial cardiovascular effects. Our results suggest that the novel long acting GLP-1/glucagon dual agonist HM12525A may have therapeutic potential and benefits in the treatment of hyperlipidemia.

1027-P

ITCA 650: A Novel Therapeutic Approach to Treating Type 2 Diabetes (T2D)

AMY WHITSON, REHAN AZEEM, TOM ALESSI, MICHELLE BARON, *Boston, MA*

ITCA 650 is a novel delivery system and GLP-1 receptor agonist that can provide continuous subcutaneous (SC) exenatide for up to 12 months after subdermal placement of a small, 4.4 cm titanium osmotic mini-pump. Three and 6 month mini-pumps were studied in clinical trials of 39 weeks or more that showed significant reductions in HbA1c and body weight, and were well tolerated in pts with T2D who were uncontrolled on antidiabetes medications. This novel drug/device can ensure maintenance of therapeutic exenatide levels and virtually ensures treatment adherence. We present the procedure experience from the FREEDOM Phase 3 program. Placement and removal of ITCA 650 is performed by trained healthcare professionals (HCPs) as a simple short office procedure. The sterile mini-pump is placed in the sub-dermis of the abdominal wall using a placement tool, is removed or replaced through a small incision (~5mm) and closed with Steri-Strips. Site personnel are provided with a kit containing all supplies and are trained on all procedures via an online and hands-on training program. As of November 2015, over 18,383 ITCA 650 placements, replacements, and removals were performed in 5,200 pts by MDs, NPs, and PAs at 493 clinical sites in 28 countries. Procedure AEs were generally mild, transient, and reflect the normal healing process. Superficial skin infection occurred in 0.4% of all procedures. Approximately 1% of procedures were initially unsuccessful and required further assistance to complete; this number that continues to decrease due to an optimized training and user experience program. Next generation placement aids will support continuous improvements. To date, only 0.19% of procedure AEs (0.7% of pts) resulted in treatment discontinuation. There were no procedure SAEs. Once or twice-yearly dosing of ITCA 650 has the potential to improve therapeutic outcomes. Procedures to place, replace, and remove the mini-pumps are simple, well tolerated, and have been performed safely by a wide variety of HCPs.

Supported By: Intarcia Therapeutics, Inc.

1028-P

Impact of Baseline HbA1c, BMI, and Diabetes Duration on the Efficacy and Safety of LixiLan (Insulin Glargine/Lixisenatide Titratable Fixed-Ratio Combination) vs. Insulin Glargine and Lixisenatide in the LixiLan-O Trial

MELANIE DAVIES, LAWRENCE A. LEITER, GEORGE GRUNBERGER, F. JAVIER AMPUDIA-BLASCO, BRUNO GUERCI, CHRISTINE YU, WILLIAM STAGER, ELISABETH NIEMOELLER, ELISABETH SOUHAMI, JULIO ROSENSTOCK, LIXILAN-O TRIAL INVESTIGATORS, *Leicester, United Kingdom, Toronto, ON, Canada, Bloomfield Hills, MI, Valencia, Spain, Vandoeuvre Les Nancy, France, Bridgewater, NJ, Frankfurt, Germany, Paris, France, Dallas, TX*

LixiLan-O was an open-label trial comparing the efficacy and safety of LixiLan, a novel titratable fixed-ratio combination of insulin glargine (Gla-100) and lixisenatide, with Gla-100 alone and lixisenatide alone over 30 weeks in type 2 diabetes (T2DM) inadequately controlled on Metformin ± a second oral glucose-lowering drug. In this exploratory analysis, participants were split according to baseline characteristics: HbA_{1c} <8%, ≥8%; duration of T2DM <7, ≥7 years; and body mass index <30, ≥30 kg/m^2. LixiLan was shown to be consistently effective in all subgroups, including those with defined obesity and high HbA_{1c} (Table). Glycemic control was consistently improved with LixiLan with more responders in all subgroups, compared with the other components' subgroups. There was no increase in the incidence of hypoglycemia in the LixiLan vs. Gla-100 groups despite better glycemic control. In conclusion, LixiLan consistently improved glycemic control compared with Gla-100 and lixisenatide, without an increase in hypoglycemia risk compared with Gla-100 in all subpopulations tested, and results were consistent with those obtained for the total LixiLan-O cohort population.

Table.

Baseline characteristics subgroup (N=LixiLan/Gla-100/lixisenatide)	Parameters	LixiLan (fixed-ratio combination, QD)			Gla-100 (insulin glargine, QD)			Lixisenatide (GLP-1, QD)		
		HbA_{1c}, %	%HbA_{1c}<7*	Hypo, %† (e/p-y)	HbA_{1c}, %	%HbA_{1c}<7	Hypo, %† (e/p-y)	HbA_{1c}, %	%HbA_{1c}<7	Hypo, %† (e/p-y)
HbA_{1c} <8% (N=222/223/109)	BL	7.5	83.8	23.0 (1.3)	7.5	67.7	22.4 (1.4)	7.5	50.5	5.5 (0.2)
	Week 30	6.3			6.7			7.0		
	Change	−1.2			−0.8			−0.5		
for Resp/Hypo (N=222/223/110)	‡Diff				−0.3±0.1	16.0±4.0		−0.7±0.1	33.3±5.2	
HbA_{1c} ≥8% (N=245/241/124)	BL	8.6	69.8	27.9 (1.6)	8.6	53.9	24.6 (1.1)	8.7	19.4	7.3 (0.5)
	Week 30	6.7			7.0			7.6		
	Change	−1.9			−1.6			−1.1		
for Resp/Hypo (N=247/244/123)	‡Diff				−0.3±0.1	16.5±4.4		−0.8±0.1	51.4±4.5	
Duration of diabetes <7 years (N=202/210/96)	BL	8.0	75.2	21.3 (1.3)	8.1	61.9	19.0 (0.8)	8.0	37.5	7.3 (0.3)
	Week 30	6.5			6.9			7.2		
	Change	−1.5			−1.2			−0.8		
for Resp/Hypo (N=202/210/96)	‡Diff				0.3±0.1	13.8±4.5		0.7±0.1	38.9±5.4	
Duration of diabetes ≥7 years (N=265/254/137)	BL	8.1	72.6	28.8 (1.6)	8.1	57.4	27.2 (1.6)	8.2	29.9	5.8 (0.4)
	Week 30	6.6			6.8			7.4		
	Change	−1.6			−1.3			−0.8		
for Resp (N=266/256/137)	‡Diff				0.3±0.1	15.5±4.1		0.8±0.1	43.2±4.6	
for Hypo (N=267/257/137)										
BMI <30 kg/m^2 (N=173/178/74)	BL	8.1	78.6	31.6 (2.2)	8.1	57.9	29.1 (1.8)	8.1	28.4	12.0 (0.8)
	Week 30	6.5			6.9			7.4		
	Change	−1.6			−1.2			−0.7		
for Resp/Hypo (N=174/179/75)	‡Diff				−0.4±0.1	20.3±4.7		−0.9±0.1	50.4±5.8	
BMI ≥30 kg/m^2 (N=294/286/159)	BL	8.1	75.2	22.0 (1.0)	8.1	62.2	20.1 (0.9)	8.1	36.5	3.8 (0.1)
	Week 30	6.6			6.8			7.3		
	Change	−1.5			−1.3			−0.8		
for Resp/Hypo (N=295/288/158)	‡Diff				−0.3±0.1	13.3±3.8		−0.7±0.1	38.4±4.3	

All data are mean unless stated otherwise
*Responders are defined as patients who achieved HbA_{1c} <7% at Week 30
†Incidence of documented symptomatic hypoglycemia (% of patients experiencing hypoglycemia, where hypoglycemia is defined as an event with typical symptoms accompanied by a measured plasma glucose concentration of ≤70 mg/dL [≤3.9 mmol/L])
‡Diff=mean difference LixiLan versus Gla-100 or Lixisenatide±SE
BL=baseline; BMI=body mass index; e/p-y=events per patient-year; Gla-100=insulin glargine; HbA_{1c}=glycated hemoglobin; Hypo=hypoglycemia; Resp=responders; SE=standard error

Supported By: Sanofi

1029-P

Tolerability, Safety, Pharmacokinetics, and Therapeutic Efficacy of Once-Weekly Administration of GLP-1 Analogue in T2DM Patients

EDY LIU, XIAOHUI GUO, GREGORY TRACEY, MICHAEL WILLETT, KENNETH LASSETER, GAVIN HUANG, WEI LV, JOE ZHOU, LIHONG ZHANG, MICHAEL M. XU, *Suzhou, China, Beijing, China, Secaucus, NJ, Miami, FL*

Exenatide is a 39-amino-acid peptide approved for the treatment of type 2 diabetes. To overcome the short half-life and alleviate the side effects associated with exenatide, we developed a long-acting form of exenatide (PB-119) by site-specific PEGylation. The tolerability, safety and pharmacokinetics of PB-119 have been evaluated in healthy volunteers. This study aimed to further evaluate the therapeutic efficacy, in addition to the safety, tolerability, and pharmacokinetics of multiple doses of PB-119 in T2DM patients in China and U.S. In a placebo-controlled, randomized, double-blind study involving 30 subjects with T2DM (10 subjects/cohort), 24 subjects were randomized to receive PB-119 with or without Metformin and 6 subjects were randomized to receive placebo for 4 weeks. It was found that PB-119 was well tolerated for the dosage studied (25 μg, 50 μg and 100 μg). The pharmacokinetic characteristics and the therapeutic efficacy as indicated by the plasma glucose and fructosamine levels confirmed the feasibility of once weekly administration of PB-119 in clinical practice.

Furthermore, 36 T2DM patients were randomized into 2 groups to receive weekly subcutaneous administration of PB-119 (25 μg and 50 μg) for 3 months (18 subjects/group, 6 subjects/group received twice daily administration of exenatide (Byetta)). The occurrences of immunogenicity and GI side effects (such as nausea and vomiting) were significantly reduced in patients treated with PB-119 compared with the Byetta group. Linear pharmacokinetics profile was observed. Once-weekly administration of PB-119 significantly reduced fasting and postprandial glucose and increased insulin and C-peptide AUC. Reductions of HbA1c were observed in a similar level compared with Byetta group.

In conclusion, alleviated adverse events (including nausea and vomiting), less dosing frequency (once weekly) and comparable therapeutic efficacy compared with Byetta can be achieved by PB-119.

1030-P

Evaluation of Novel Short- and Long-Acting G-protein Biased GLP-1R Agonists for the Treatment of T2DM

EMMANUEL STURCHLER, HONGKAI ZHANG, JIA XIE, PHILIP E. DAWSON, RICHARD A. LERNER, PATRICIA H. MCDONALD, *Jupiter, FL, La Jolla, CA*

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by hyperglycaemia arising from a combination of insufficient insulin secretion and the development of insulin resistance. Glucagon-like peptide-1 (GLP-1) mimetics have emerged as attractive treatment options for T2DM. Currently approved GLP-1R agonists are either short acting molecules requiring daily dosing or long acting molecules allowing for once-weekly dosing. Although these treatments demonstrate remarkable antidiabetic activity, adverse side effects and concerns regarding safety profile following prolonged use of GLP-1R based therapeutics have emerged. The GLP-1R signals via G-proteins and β-arrestins, as such the pleiotropic signaling capacity of this receptor may be responsible for the unwanted side effects. Recent clinical success has revealed that GPCR biased ligands can offer improved efficacy with reduced toxicity. We have identified and characterized a short- and a long acting G-protein biased GLP-1R agonist, P5 and P5-Fc respectively. *In vitro*, both peptides promoted G-protein signaling comparable to GLP-1 or the GLP-1 mimetic exendin-4, but exhibited a significantly attenuated β-arrestin response. Preclinical studies in mouse models of T2DM demonstrated that P5 is a weak insulin secretagogue yet provides improved long term glycemic control compared to exendin-4. In addition, daily injection of P5 promoted adipocyte hyperplasia, decreased inflammation, and restored insulin responsiveness in white adipose tissue. A single injection of P5-Fc increased glucose tolerance in metabolically healthy mice as well as in diet-induced obese mice and this effect persisted over 6 days. Daily dosing with P5 did not promote satiety nor weight loss whereas bi-weekly treatment with P5-Fc resulted in a significant reduction in body weight. Thus, P5 and P5-Fc display novel and distinct mechanisms of action and may provide novel therapeutic approaches for the treatment of T2DM.

1031-P

Efficacy and Safety by Gender across the Different Treatments in the Dulaglutide AWARD Program

LUIS-EMILIO GARCÍA-PÉREZ, KENNETH E. ROBERTSON, MARIA YU, NAN ZHANG, VIVIAN T. THIEU, *Indianapolis, IN, Toronto, ON, Canada*

Dulaglutide (DU), a once weekly GLP-1 receptor agonist, was studied in the AWARD clinical trial program in adult patients (pts) with T2D and demonstrated significant A1c reduction and potential for weight loss.

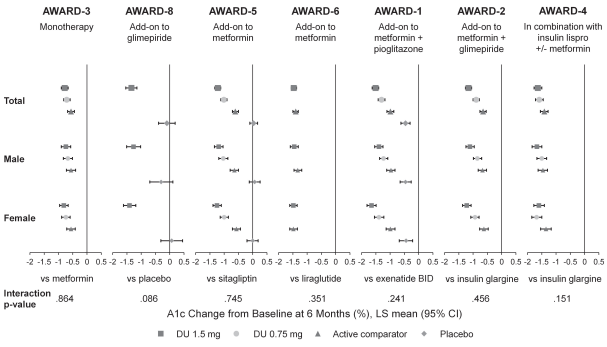
To evaluate the efficacy and safety of DU and active comparators (AC) in male and female pts, we conducted a post-hoc analysis on AWARD-1 to 6 and 8 at 6 months. Data are reported per trial due to differences in designs, background therapies, and baseline characteristics.

Across the 7 studies, the proportions of male and female were similar. The ranges of A1c changes in male and female, respectively, were: DU 1.5 mg: -0.74 to -1.67%, -0.81 to -1.65%; DU 0.75 mg: -0.67 to -1.50%, -0.74 to -1.68%; AC: -0.56 to -1.46%, -0.56 to -1.48%. The ranges of weight changes in male and female, respectively, were: DU 1.5 mg: -0.24 to -2.56 kg, -0.75 to -3.77 kg; DU 0.75 mg: +0.61 to -1.97 kg, +0.25 to -3.20 kg; AC: +2.34 to -2.91 kg, +2.20 to -4.21 kg. The magnitudes of A1c reductions were similar between male and female (Figure). In general, females had a numerically greater weight loss or less weight gain than males across all treatments and studies except DU 0.75 mg and exenatide BID in AWARD-1. All treatments were well tolerated, and females, in general, had numerically higher incidences of nausea and vomiting.

Across all treatments and studies, A1c reduction was similar between male and female with an acceptable safety profile.

For author disclosure information, see page A696.

Figure.



Supported By: Eli Lilly and Company

1032-P

Effect of Once-Weekly Dulaglutide by Baseline β-Cell Function in the AWARD Program

CHANTAL MATHIEU, FADY T. BOTROS, VIVIAN THIEU, NAN JIA, NAN ZHANG, LUIS-EMILIO GARCIA-PEREZ, *Leuven, Belgium, Indianapolis, IN*

Dulaglutide (DU), a once weekly GLP-1 receptor agonist, was studied in the AWARD clinical trial program in adult patients (pts) with T2D and demonstrated significant A1c reduction and potential for weight loss. A pooled post-hoc subgroup analysis was conducted on studies AWARD-1, 3, 5 and 6 to evaluate the effects of DU by baseline β-cell function (as estimated by HOMA2-%B). Pts were categorized into three subgroups defined by tertiles (low, medium, high) of baseline HOMA2-%B. Fasting c-peptide was available for AWARD-1, 3, and 6 (low, n=440; medium, n=459; high, n=447), and fasting insulin was available for AWARD-1, 3, and 5 (low, n=495; medium, n=510; high, n=496), to calculate HOMA2-%B. Across DU arms of these trials, pts had a mean baseline age of 54-57 years, duration of diabetes of 3-9 years, A1c of 7.6-8.2%, and BMI of 31-34 kg/m^2. In the subgroups of pts with lower HOMA2-%B, fasting c-peptide and insulin was generally lower, while baseline fasting glucose, A1c, and duration of diabetes tended to be higher compared to the subgroups of pts with higher baseline HOMA2-%B (Table). Reductions of A1c from baseline to week 26 in response to DU treatment tended to be greater in the higher HOMA2-%B tertiles, but the differences were small and may have limited clinical relevance (Table). In conclusion, pts treated with DU demonstrate clinically relevant A1c reductions regardless of estimated baseline β-cell function.

Table. Pooled Analysis on Baseline Characteristics and A1c Change from Baseline by HOMA2-%B.

HOMA2-%B Tertiles, Mean (SD)		Baseline Characteristics, Mean (SD), ITT				A1c Change at 26 Weeks (%), Mean (95% CI), ITT, LOCF	
		Fasting c-peptide (nmol/L) or insulin (pmol/L)	Fasting Blood Glucose (mg/dL)	A1c (%)	Duration of diabetes (years)	DU 1.5 mg	DU 0.75 mg
HOMA2-%B (c-peptide; AWARD-1, 3, and 6; AWARD-6 did not contribute to the DU 0.75 mg data)	Low: 30.4 (9.5)	0.7 (0.3)	203.3 (49.9)	8.7 (1.1)	7.7 (6.0)	-1.00 (-1.13, -0.88)	-0.72 (-0.88, -0.56)
	Medium: 57.9 (8.4)	0.9 (0.4)	158.0 (34.7)	7.7 (0.9)	5.9 (5.2)	-1.03 (-1.14, -0.92)	-0.94 (-1.08, -0.79)
	High: 109.1 (38.3)	1.3 (0.6)	127.2 (23.5)	7.2 (0.7)	4.6 (4.1)	-1.18 (-1.31, -1.05)	-0.91 (-1.04, -0.78)
HOMA2-%B (insulin; AWARD-1, 3, and 5)	Low: 22.8 (8.5)	63.6 (35.6)	210.7 (54.8)	8.8 (1.2)	8.1 (5.8)	-0.98 (-1.11, -0.85)	-0.78 (-0.91, -0.65)
	Medium: 50.0 (8.4)	98.2 (49.2)	155.9 (33.8)	7.7 (0.8)	6.0 (4.6)	-0.98 (-1.10, -0.86)	-0.89 (-1.01, -0.77)
	High: 103.2 (38.1)	157.4 (72.0)	128.9 (23.3)	7.3 (0.7)	4.4 (4.0)	-1.09 (-1.21, -0.96)	-0.84 (-0.97, -0.72)

Supported By: Eli Lilly and Company

1033-P

The Dual Amylin- and Calcitonin Receptor Agonist KBP-042 Is an Insulin Sensitizer with a Weight-Reducing Effect

SARA T. HJULER, SOFIE GYDESEN, KIM V. ANDREASSEN, MORTEN A. KARSDAL, KIM HENRIKSEN, *Herlev, Denmark*

Overweight and obesity are often associated with decreased insulin sensitivity. Insulin sensitizers that can reduce body weight and increase glucose tolerance and insulin action are needed. KBP-042 is a dual amylin- and calcitonin receptor agonist with potential for treating metabolic disorders. In this study we evaluated the insulin sensitivity in rats after treatment with KBP-042. 6 weeks old Sprague-Dawley rats fed a high fat-diet (HFD) or standard rodent chow (ND) for ten weeks were stratified into groups according to body weight: ND-Vehicle, HFD-Vehicle and HFD-KBP-042 (5 µg/kg). The rats were dosed s.c. in the afternoon with drug or saline for 3 weeks. Hyperinsulinemic-euglycemic clamps (HIEC) were performed to evaluate glucose infusion rate (GIR) as a measure of insulin sensitivity. One week before the clamp, animals were anaesthetized with a fentanyl/fluanisone + midazolam mixture and catheters were placed in the femoral and jugular veins for infusion and blood sampling, respectively. Prior to the HIEC, animals were fasted 4-5 hours and then infused with 0.4 U/kg/h human insulin (20 µl/min) and varying infusion rates of D-glucose (30% w/v). The rate of glucose sufficient for stabilizing blood glucose at initial fasting level relative to the body weight was considered GIR. High fat feeding significantly increased body weight compared to ND (11.3%, p<0.05). The treatment with KBP-042 reduced the body weight (17%, p<0.01) compared to HFD-Vehicle. ND-Vehicle and KBP-042 treated groups did not have significant different body weight. In the HIEC, KBP-042 treatment improved GIR with 82% (p<0.001) and 27% (p<0.05) when compared to HFD-Vehicle and ND-Vehicle, respectively. KBP-042 efficiently reduced body weight and improved insulin sensitivity in a HIEC. The ability to simultaneously lower body weight and insulin resistance makes KBP-042 a promising drug candidate for the treatment of obesity-related insulin resistance and type 2 diabetes.

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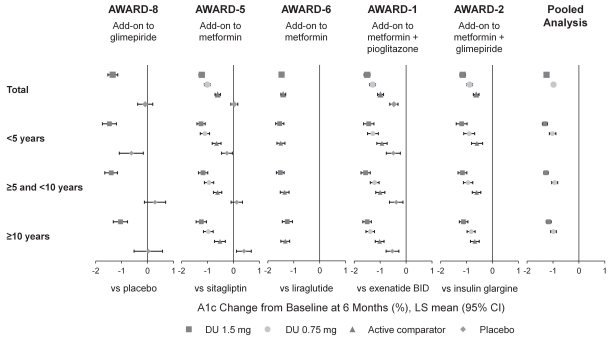
1034-P

Efficacy and Safety by Duration of Diabetes with Once-Weekly Dulaglutide in the AWARD Program

BAPTIST GALLWITZ, IMRE PAVO, VIVIAN THIEU, NAN JIA, NAN ZHANG, LUIS-EMILIO GARCIA-PEREZ, *Tübingen, Germany, Vienna, Austria, Indianapolis, IN*

Dulaglutide (DU), a once weekly GLP-1 receptor agonist, was studied in the AWARD clinical trial program in adult patients (pts) with T2D and demonstrated significant A1c reduction and potential for weight loss. To evaluate the efficacy and safety of DU 1.5 mg and DU 0.75 mg in T2D pts by duration of diabetes (DoD) <5 years, ≥5 and <10 years, and ≥10 years, we conducted a post-hoc analysis on the completed studies AWARD-1, 2, 5, 6 and 8 at 6 months. AWARD-3 and 4 were not included in the analysis because, due to the population studied, small numbers of pts had DoD ≥10 years in AWARD-3 and DoD <5 years in AWARD-4. Across the 5 studies, the proportions of pts with DU treatment were similar among DoD subgroups. The ranges of A1c reductions with DoD <5 years, ≥5 and <10 years, and ≥10 years, respectively, were: DU 1.5 mg: -1.19 to -1.54%, -1.16 to -1.56%, and -1.04 to -1.50%; DU 0.75 mg: -0.90 to -1.28%, -0.94 to -1.21%, and -0.82 to -1.38%. The A1c changes were similar from the pooled analysis with DoD <5 years, ≥5 and <10 years, and ≥10 years: DU 1.5 mg: -1.31%, -1.27%, and -1.17%; DU 0.75 mg: -1.02%, -0.93%, and -0.98%, respectively (Figure). The effects on weight were similar among DoD subgroups with both DU doses, respectively. DU treatments were well tolerated among DoD subgroups. In conclusion, irrespective of DoD, pts treated with DU demonstrate similar A1c reduction, weight change, and acceptable safety profile.

Figure.



Supported By: Eli Lilly and Company

1035-P

Continuous Delivery of Exenatide by Subdermal Placement of ITCA 650 in Nonhuman Primates Demonstrates Safety and Tolerability in a 9-Month Chronic Toxicity Study

DORIS T. ZANE, LAUREN THORNER, MICHELLE A. BARON, ROBERT M. FIELDING, REBECCA W. COMBA, THOMAS R. ALESSI, *Hayward, CA, Boston, MA, Boulder, CO, Reno, NV*

ITCA 650 is an osmotic mini-pump that delivers exenatide as a continuous zero-order infusion following subdermal placement. In a chronic toxicity study, cynomolgus monkeys received ITCA 650 at exenatide doses of 0, 10, 60, 160 and 240 ug/d for 9 months, with a 2 month recovery. On D1, four ITCA 650 and/or placebo were placed subdermally. At 3 months, mini-pumps were removed and replaced with another of the same dose at the same site to provide continuous exposure for an additional 6 months. At 9 months, mini-pumps were removed. Exposure multiples, from antibody-negative animals on D7, ranged from 7-times (10 ug/d) to 113-times (240 ug/d) the human systemic exposure (AUC). Most ITCA 650-treated animals developed anti-exenatide antibodies after D7, associated with increased plasma exenatide levels. There were no changes in clinical observations, electrocardiographic measurements, blood pressure, ophthalmic exams, or clinical pathology in the ITCA 650 groups compared to placebo. As expected from the pharmacology of exenatide, acute reduction in body weight and food consumption was observed wk 1 which did not persist beyond wk 2. No test article-related gross, organ weight, or microscopic changes were observed. At the end of the terminal phase (D280), incidence and severity of microscopic changes representative of a minimal localized tissue response at the placement sites were similar between placebo and ITCA 650 groups. At the end of the recovery phase (D336), resolving tissue response consisting of microscopic changes at the placement sites were similar between placebo and ITCA 650 groups. Based on these results, the no-observed-adverse-effect level (NOAEL) was 240 ug/d. The exposures achieved at the NOAEL were substantial multiples of the anticipated clinical dose at 60 ug/d. These data support the clinical findings of safety and local tolerability at the site of administration after repeated placement and removal of ITCA 650.

1036-P

Change in HbA1c, Weight, and Blood Pressure in the Association of British Clinical Diabetologists (ABCD) Nationwide Exenatide Once Weekly (QW) Audit

ROBERT M. GIFFORD, JALINI JOHARATNAM, KEN DARZY, AHMED HELMY, EDWARD MCKEEVER, URSULA BRENNON, ROY HARPER, KEITH SANDS, DENNIS BARNES, ROBERT E. RYDER, KAREN A. ADAMSON, *Livingston, United Kingdom, Welwyn Garden City, United Kingdom, Enniskillen, United Kingdom, Dundonald, United Kingdom, Barnsley, United Kingdom, Tunbridge Wells, United Kingdom, Birmingham, United Kingdom*

Background: The Association of British Clinical Diabetologists (ABCD) conducted a nationwide audit of exenatide once weekly (QW) treatment.

Methods: 19 centres across the UK submitted anonymised data on 441 patients commencing exenatide QW. Baseline and on-treatment HbA1c, weight, BMI, blood pressure and changes in medication were examined. Patients were excluded on the basis of no follow-up data and extreme values for BP, BMI, weight or HbA1c. Data at baseline and first follow-up were compared using student's paired t-test.

Results: Baseline characteristics were 50.6% male, 62.7% British ethnicity, mean (SD) age 56.3 (10.4) years, HbA1c 9.45 (1.85)%, weight 108.5 (23.4) kg, BMI 37.9 (7.72) kg/m2, BP 135.2 (22.3)/79.8 (10.6) mmHg, median (interquartile range) diabetes duration 11 (7-17) years.

Data from first review at least 3 months from commencing exenatide QW were examined (data recorded for 304 patients). Median (interquartile range) duration to first follow up interval was 6 (4-10) months, range 3-32 months. Mean (SD) HbA1c change at first follow-up was -0.83 (1.71)%, 95% CI 0.64 - 1.02%, (P<0.0001). Mean weight change from baseline to first follow-up was -1.39 (9.91) kg, 95% CI 0.28-2.49kg, P <0.05, and BMI -0.40 (3.19) kg/m2, 95% CI 0.04 - 0.76 (P<0.05). Systolic blood pressure was modestly lower at first review (mean (SD) -2.30 (17.4) mmHg (95% CI 0.18-4.41mmHg, P<0.05), but not diastolic blood pressure.

Conclusion: These data suggest a more modest reduction in HbA1c, weight and BMI with exenatide QW, compared with data from national audits of GLP-1 analogues. A 2.3mmHg reduction in systolic blood pressure was demonstrated. Our real-world data are limited by their retrospective nature, potential unknown confounders such as patient concordance, which were not assessed, and relatively low patient numbers.

1037-P

YH25723, a Novel Long-Acting GLP-1/FGF-21 Dual Agonist Provides More Potent and Sustained Glycemic Control and Greater Weight Loss Compared with Single Agonists in Animal Models

JUN H. KIM, HYUN H. CHOI, DOHOON KIM, SEYOUNG LIM, MINJI SEO, MI K. JU, JU-YOUNG PARK, BYUNG H. CHOI, JONG G. KIM, SU Y. NAM, *Seoul, Republic of Korea*

Targeting multiple metabolic pathways provides better therapeutic potential compared to molecules targeting a single pathway, because metabolic disorders are triggered by various complicated factors. GLP-1 receptor agonists have been developed and approved for the treatment of type 2 diabetes given their benefit from the glucose-dependent insulinotropic effects of GLP-1. Fibroblast growth factor 21 (FGF-21) is a promising drug candidate for the treatment of metabolic diseases, which enhances insulin sensitivity. Thus, a complementary and synergistic therapeutic potential is anticipated by combining GLP-1 and FGF-21 agonism. YH25723 is a novel long-acting dual agonist, which is an immunoglobulin Fc-fused protein comprising GLP-1 variant and FGF-21 variant. To evaluate the pharmacokinetic (PK) profile of the dual agonist, multi-ELISA method was developed to detect each active moiety. Based on mouse PK data, the YH25723 has an optimal PK profile for once-weekly dosing in human. YH25723 exhibited potent and sustained glycemic control and weight loss in three rodent models. After single subcutaneous injection in db/db mice and low-dose streptozotocin-treated mice fed with high-fat diet, the dual agonist elicited rapid, potent, sustained and dose-dependent glucose-lowering and profound weight loss compared to single agonism (GLP-1 or FGF-21 agonist) or dulaglutide. Following repeat dosing in diet-induced obese mice, the dual agonist produced a synergistic effect on body weight loss compared to single agonism and more potent and sustained body weight loss compared to dulaglutide. Furthermore, *ex vivo* T cell activation assays indicate that the dual agonist has a low potential risk for clinical immunogenicity. These findings indicate that YH25723, a novel long-acting GLP-1/FGF-21 dual agonist would be a novel therapeutic for the treatment of metabolic diseases including type 2 diabetes and obesity.

Supported By: Korea Health Industry Development Institute

1038-P

Lixisenatide (Lyxumia®) Has No Effect on QTc Interval in Healthy Subjects: A Thorough QTc Study

JOACHIM TILLNER, GEORG GOLOR, PASCAL VOIRIOT, ANNE LEHMANN, CHRISTIANA FROSIO, CATHERINE MEGARD, MARTIN LORENZ, *Frankfurt, Germany, Berlin, Germany, Nancy, France, Chilly Mazarin, France*

Lixisenatide is a once-daily (QD) short-acting GLP-1 agonist for the treatment of type 2 diabetes mellitus. Aim of this thorough QTc study was to assess the effect of a therapeutic and a supratherapeutic dose regimen of lixisenatide on QTcF and other ECG parameters (HR, QT, QTcB, QTcN, PR and QRS) in healthy subjects. The study was a single-center, multiple dose, randomized, double-blind, double-dummy, placebo controlled study with moxifloxacin 400 mg as a positive control, conducted in 4 parallel groups with a total of 264 healthy subjects stratified by gender. Groups were treated with: 1.) Lixisenatide 10 - 15 - 20 µg s.c. QD, 2.) Lixisenatide 10 - 20 - 30 µg s.c. BID, 3.) placebo s.c., 4.) placebo s.c. + 400 mg moxifloxacin (single dose on Day 28). Treatment duration was 28 days (7 - 7 - 14 days). The assessment of ventricular repolarization was performed using 24-hour continuous 12-lead Holter-ECG recordings on Days 1 and 28. Triplicate 10-second recordings were extracted from the Holter records at prespecified time points ranging from 30 minutes before up to 24 hours after drug administration. Intervals were derived thereof by semi-automatic reading. Largest time-matched mean difference (LTMMD) in heart rate at 4hrs post dose were 7.29 bpm for 20 µg QD and 8.63 bpm for 30 µg BID. HR increases were transient and returned close to baseline after 12 hours. Baseline and placebo adjusted 24h mean heart rate increase was 1.3 bpm for 20 µg QD and 3.2 bpm for 30 µg BID lixisenatide. The baseline and placebo corrected LTMMD estimate for QTcF on Day 28 was 4.60 ms for lixisenatide 20 µg QD (90% CI: 2.34 to 6.87 ms) and 5.48 ms for 30 µg BID (90% CI: 3.22 to 7.75 ms). The E14 criteria for a negative study outcome in terms of QT interval prolongation were met as for both lixisenatide groups the upper bound of the 90% 2 sided CI for the LTMMD on the QTcF interval was < 10 ms, confirming that lixisenatide has no clinically relevant effect on ventricular repolarization.

Supported By: Sanofi

For author disclosure information, see page A696.

1039-P

Baseline Characteristics of Patients Enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL)

ROBERT MENTZ, M. ANGELYN BETHEL, STEPHANIE GUSTAVSON, VIVIAN THOMPSON, JOHN B. BUSE, JULIANA CHAN, ALDO P. MAGGIONI, STEVEN P. MARSO, PETER OHMAN, NEIL POULTER, AMBADY RAMACHANDRAN, BERNARD ZINMAN, NAYYAR IQBAL, ADRIAN F. HERNANDEZ, RURY R. HOLMAN, *Durham, NC, Oxford, United Kingdom, Gaithersburg, MD, Chapel Hill, NC, Hong Kong, China, Florence, Italy, Kansas City, MO, London, United Kingdom, Chennai, India, Toronto, ON, Canada*

EXSCEL is a double-blind, placebo-controlled trial examining the effect of a once-weekly injection of exenatide vs. placebo on time to the primary composite outcome (cardiovascular [CV] death, nonfatal myocardial infarction or nonfatal stroke).

Eligible patients had type 2 DM and a wide range of CV risk, randomization targeted 70% with a history of a CV event (coronary artery disease [CAD], cerebrovascular disease or peripheral arterial disease [PAD]). We describe the baseline characteristics of participants according to their CV event status.

Of 14,753 participants randomized between June 2010 and September 2015, 73% had a prior CV event (70% CAD, 24% PAD, 22% cerebrovascular). The median (IQR) age was 63 yrs (56, 69), 38% were female, and 16% had a prior history of heart failure. The median (IQR) HbA1c, diabetes duration, and BMI were 8.0% (7.3, 8.9), 12 (7, 18) yrs, and 32 (28, 36) kg/m^2, respectively. Patient characteristics by prior CV event status are presented in the Table.

EXSCEL is one of the largest ongoing GLP-1 receptor agonist trials, evaluating the effect of once weekly exenatide on CV safety and efficacy. Unique characteristics include a substantial percentage of patients with no prior CV event, and a notable percentage who were taking a DPP-IV inhibitor at baseline.

Table. Baseline Characteristics by Prior CV Event Status.

	All Participants (N=14,753)	Prior CV Event (N=10,784)	No Prior CV Event (N=3,969)
Systolic blood pressure, mmHg	135 (124, 145)	135 (124, 146)	134 (124, 144)
LDL, mg/dL	88 (67, 117)	84 (64, 112)	99 (75, 126)
Antiplatelet therapy	70%	81%	40%
Lipid lowering agent	77%	82%	62%
Metformin	77%	73%	85%
DPP-IV Inhibitors	15%	14%	17%
Insulin	46%	52%	32%

Presented as % or median (IQR).

1040-P

Long-Term Treatment with Injectable Testosterone Undecanoate (TU) Improves Type 2 Diabetes (T2DM) and Mortality in Hypogonadal Men

FARID SAAD, AHMAD HAIDER, GHEORGHE DOROS, ABDULMAGED TRAISH, *Berlin, Germany, Bremerhaven, Germany, Boston, MA*

Registry in 656 hypogonadal men, 230 with T2DM. 113 received TU 1000 mg/12 weeks, 117 CTRL. Measurements twice a year for 8 years. Mean changes over time between groups were compared by mixed effects model for repeated measures with random effect for intercept and fixed effects for time, group and their interaction. Changes were adjusted for age, weight, waist circumference, HbA_{1c}, blood pressure (BP), lipids to account for baseline differences between the two groups. Age: 63.4±4.7 years. Glycemic control improved in T Group, worsened in CTRL. Anthropometric parameters improved in T Group, worsened in CTRL. Model-adjusted estimated difference between groups at 8 years was significant for all measures. Total, LDL cholesterol, triglycerides decreased in T Group, increased in CTRL. HDL improved significantly in both groups. Systolic BP improved in T group ($p<0.0001$), increased in CTRL ($p<0.05$), diastolic decreased in T group ($p<0.0001$), remained stable in CTRL. Since injections were administered in the doctor's office and no patient dropped out, there was a 100% adherence to TTh. 1 patient (0.9%) in T group died. In CTRL, 14 myocardial infarctions (12%), 16 strokes (13.7%), and 9 deaths (7.7%) occurred. Long-term TTh with TU in hypogonadal men with T2DM improved diabetic and anthropometric measures and reduced major adverse cardiovascular events compared to untreated controls.

Table. Changes of Selected Parameters Over Time.

	baseline ± SD	year 1	year 2	year 3	year 4	year 6	year 8
fasting glucose (mmol/L) (CTRL)	6.24±0.79 (5.83±0.31)	5.79±0.65 (5.85±0.27)	5.5±0.44 (5.86±0.27)	5.36±0.29 (5.86±0.32)	5.33±0.18 (5.82±0.3)	5.31±0.1 (5.83±0.28)	5.23±0.05 (5.83±0.34)
HbA1c (%) (CTRL)	8.03±0.83 (7.44±0.66)	7.53±0.71 (7.53±0.69)	7.04±0.64 (7.58±0.66)	6.77±0.57 (7.71±0.65)	6.51±0.52 (7.77±0.59)	6.18±0.51 (7.9±0.63)	5.77±0.43 (8.01±0.78)
weight (kg) (CTRL)	112.53±13.2 (96.92±10.23)	108.76±12.51 (97.3±10.39)	103.68±11.83 (97.5±10.46)	100.37±10.89 (97.69±10.57)	98.63±9.83 (97.66±10.32)	94.86±8.8 (97.91±9.98)	91.79±8.97 (96.86±9.01)
LDL (mmol/L) (CTRL)	4.77±0.74 (4.17±1.57)	4.34±0.68 (4.41±1.56)	3.98±0.72 (4.48±1.56)	3.85±0.71 (4.55±1.55)	3.7±0.68 (4.6±1.54)	3.55±0.63 (4.79±1.62)	3.03±0.63 (4.73±1.48)
blood pressure (mmHg) (CTRL)	161.79/96.77 (140.62/80.26)	153.34/89.91 (140.51/80.35)	146/84.06 (141/81.09)	141.37/80.79 (140.97/80.78)	139.45/79.54 (140.35/81.15)	137.19/77.74 (139.53/81.26)	131.07/74.48 (144.36/82.91)
CRP (mg/dl) (CTRL)	4.31±5.6 (1.14±1.11)	3±3.43 (0.97±0.76)	1.76±2 (0.92±0.8)	1.22±1.69 (0.94±0.64)	0.79±1.12 (0.89±0.62)	0.5±0.78 (1.03±0.66)	0.3±0.39 (1.39±0.95)
testosterone (nmol/L) (CTRL)	9.93±1.12 (9.77±1.2)	16.03±1.91 (9.79±0.77)	17.27±1.96 (9.55±1.01)	17.04±1.75 (9.43±0.98)	17.18±1.79 (9.54±0.95)	16.25±1.34 (9.44±1.07)	16.45±1.41 (8.79±1.51)

Supported By: Bayer HealthCare

1041-P

DURATION-1 Extension in Patients with T2D: Efficacy and Tolerability of Exenatide Once Weekly (QW) Over 7 Years

CAROL H. WYSHAM, ATHENA PHILIS-TSIMIKAS, ERIC J. KLEIN, PETER ÖHMAN, NAYYAR IQBAL, JENNY HAN, ROBERT R. HENRY, *Spokane, WA, San Diego, CA, Olympia, WA, Gaithersburg, MD*

Lifelong pharmacotherapy for T2D is anticipated, but >1-2 y efficacy and safety data are uncommon. DURATION-1 compared exenatide QW and twice daily in 295 patients over 30 wk, after which all patients received exenatide QW; we report 7 y safety (ITT) and efficacy (122 completers [41%)] data. Withdrawal reasons included withdrawn consent (27%), AE (12%), investigator decision (7%), lost to follow-up (7%), and glucose control lost (4%). Baseline mean age was 56 y and T2D duration was 7 y. Concomitant medications included MET (84%), SU (59%), and TZD (24%); 2% added long-acting insulin in Y2-Y5, 9% in Y6, and 12% in Y7. 65 patients (53%) did not initiate new glucose-lowering medication. A1c, FPG, and weight improved from baseline at 7 y (Table); 46% had A1c <7.0% and 30% had A1c ≤6.5%. Mild gastrointestinal and injection site AEs primarily occurred in the initial 30 wk. No major hypoglycemia event was reported; most minor hypoglycemia events occurred with concomitant SU therapy. Serious AEs with incidence >1% included cholecystitis, cardiovascular disorders, and joint disorders. AEs of special interest included pancreatitis (n=2 events), pancreatic cancer (n=1), and acute renal failure (n=6). In summary, exenatide QW therapy for 7 y was associated with significant, sustained reductions in A1c and weight, with infrequent insulin initiation and no new long-term safety findings.

Table.

Parameter	Baseline, Mean ± SE	7 Years, Mean ± SE	Change from Baseline, LS mean (95% CI)
A1c (%)*	8.2 ± 0.1	7.1 ± 0.1	-1.5 (-1.8, -1.3)
FPG (mg/dL)	166 ± 4	147 ± 4	-24 (-33, -14)
Body weight (kg)	101.2 ± 1.6	97.1 ± 1.6	-3.9 (-5.4, -2.4)
HOMA-B (%)	51.8 ± 3.0**	63.5 ± 3.6**	+26% (+10%, +44%)†
Systolic blood pressure (mm Hg)	128.0 ± 13.4‡	129.1 ± 15.4‡	+1.2 ± 16.7‡
Heart rate (beats per min)	73.2 ± 9.1‡	74.4 ± 10.1‡	+1.2 ± 10.1‡

CI, confidence interval; HOMA-B, homeostatic model assessment of beta cell function; LS, least squares; SD, standard deviation; SE, standard error.
*Determined by ANOVA. Secondary endpoints determined by ANCOVA.
**Geometric mean ± SE. †Percent increase from baseline based on geometric LS mean ratio of Year 7 to baseline (95% CI). ‡Mean ± SD.

Supported By: AstraZeneca; Bristol-Myers Squibb

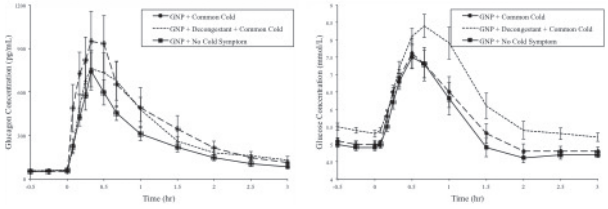
1042-P

Effects of Nasal Congestion from Common Cold on the PK and PD of Glucagon Nasal Powder

HELENE DULUDE, ERIC SICARD, MARIANNE RUFIANGE, AZIZ SADOUNE, DOLORES CARBALLO, MYRIAM TRIEST, MARYAM TAFRESHI, EMMANOUIL RAMPAKAKIS, CLAUDE A. PICHE, *Montreal, QC, Canada, Laval, QC, Canada*

Glucagon nasal powder (GNP), a needle-free glucagon that is absorbed through the nasal mucosa, is being developed to treat severe hypoglycemia. This single center, open-label study evaluated the safety, PK and PD of GNP in 36 otherwise healthy subjects with nasal congestion from common cold with or without concomitant nasal decongestant. Cohort 1 (N=18) received two GNP doses: a 3mg dose while suffering from common cold and a second 3mg dose after return to normal health. Cohort 2 (N=18) received a single 3mg dose of GNP 2 hrs after receiving the nasal decongestant oxymetazoline while suffering from common cold. There were no serious adverse events (AE); the most common AEs were transient lacrimation, nasal discomfort, rhinorrhea and nausea with reduced nasal symptoms and nausea in participants with normal health vs. those with cold symptoms, with or without decongestant. Glucagon and glucose levels increased rapidly after treatment to peak glucagon levels at 20 min post dose and peak glucose levels at 30 to 40 min post dose for all groups (Figure 1). Nasal congestion, with or without concomitant use of a nasal decongestant, did not significantly affect the PK and PD of GNP although transient AEs were more frequent in participants with common cold than in healthy participants. These data suggest that GNP can be used to treat severe hypoglycemia in patients with nasal congestion.

Figure 1. Mean (SE) Blood Glucagon (L) and Glucose (R) Levels.



Supported By: Locemia Solutions

1043-P

Efficacy and Safety of Switching from Sitagliptin (SITA) to Liraglutide (LIRA) in Subjects with Type 2 Diabetes (T2D) Not Achieving Adequate Glycemic Control on SITA and Metformin (MET): A Post Hoc Subgroup Analysis Defined by Baseline (BL) BMI < or = 30 kg/m^2

TIMOTHY S. BAILEY, RÓBERT TAKÁCS, FRANCISCO J. TINAHONES, PATURI V. RAO, GEORGE M. TSOUKAS, SIDSEL B. CHRISTENSEN, MARGIT S. KALTOFT, MAXIMO MAISLOS, *Escondido, CA, Szeged, Hungary, Malaga, Spain, Hyderabad, India, Montreal, QC, Canada, Søborg, Denmark, Beer Sheva, Israel*

This post hoc subgroup analysis of the multinational, multicenter, randomized, double-blind, active-controlled Lira-SWITCH trial compared 26 wk efficacy and safety of switching from SITA to LIRA as add-on to MET in subjects with T2D not achieving adequate glycemic control on SITA + MET, in subjects with BL BMI < or ≥30 kg/m^2.

Subjects previously receiving SITA (100 mg/day) and MET for ≥90 days, were randomized 1:1 to switch to LIRA 1.8 mg (n=203) or continue SITA 100 mg/day (n=204), both + MET.

Switching to LIRA from SITA reduced A1c (BMI <30, EM wk 26 7.08 vs. 7.73% (ETD -0.66 [95% CI -0.99;-0.32]; p=0.0001); BMI ≥30, EM wk 26 7.07 vs. 7.65% (ETD -0.58 [-0.86;-0.30]; p<0.0001)), body weight (BMI <30, EM wk 26 86.63 vs. 87.87 kg (ETD -1.24 [-2.31;-0.18]; p=0.0221); BMI ≥30, EM wk 26 86.50 vs. 88.22 kg (ETD -1.71 [-2.60;-0.82]; p=0.0002)) and FPG (Table) significantly more than continuing SITA, in both BMI groups. There were no significant differences in ETDs between BMI groups for all parameters (p>0.05) except for FPG (p=0.024).

In conclusion, switching to LIRA resulted in superior A1c and body weight reductions compared with continued SITA treatment, regardless of BL BMI status, and there was no evidence of a different treatment effect between the two BMI groups.

Table.

	BMI <30 kg/m^2			BMI ≥30 kg/m^2		
	LIRA N=87	SITA N=78	ETD [95% CI]; *p*	LIRA N=115	SITA N=126	ETD [95% CI]; *p*
FPG (mg/dL)						
Baseline*	174.75	160.64		185.78	182.38	
Week 26	146.94	162.75		139.07	161.97	
CFB	-26.28	-10.47	**-15.82** [-27.01; -4.62]; 0.0058	-34.16	-11.25	**-22.91** [-32.33; -13.49] <0.0001
SBP (mmHg)						
Baseline*	128.37	130.76		132.08	132.94	
Week 26	127.74	127.46		126.62	130.00	
CFB	-3.41	-3.70	**0.28** [-3.47; 4.03]; 0.8819	-4.53	-1.15	**-3.38** [-6.56; -0.21]; 0.0370
DBP (mmHg)						
Baseline*	77.98	78.42		79.75	79.25	
Week 26	78.15	77.63		78.97	78.61	
CFB	-0.75	-1.27	**0.52** [-1.73; 2.76]; 0.6499	0.08	-0.28	**0.36** [-1.54; 2.26]; 0.7096
Adverse events (%)	69	52.6		68.7	59.5	
Serious adverse events (%)	3.4	2.6		2.6	4.0	
Confirmed hypoglycemia†	0	0		0	3‡ (3)	

All values are estimated means (EM) unless otherwise stated. *Observed mean. †Defined as severe hypoglycemia (i.e. an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) or an episode biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia. ‡Number of subjects with confirmed hypoglycemia (number of events). BMI, body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; CFB, change from baseline (estimated means); LIRA, liraglutide; SITA, sitagliptin; ETD, estimated treatment difference.

Supported By: Novo Nordisk Inc.

1044-P

Investigation of Blood-Brain Barrier Penetration of Albiglutide in Mice

CHARLES S. HOTTENSTEIN, MATTHEW E. SZAPACS, CURTIS C. MAIER, *King of Prussia, PA*

The potential for albiglutide (ALBI) to act centrally by crossing the blood-brain barrier was assessed in a pharmacokinetic (PK) radiolabeling study in mice after subcutaneous administration of ^{125}I-ALBI, with ^{125}I-albumin or ^{125}I-transferrin dosed as comparators. Quantitation of radioactivity in plasma and brain homogenates allowed systemic PK parameters to be calculated along with distribution to the brain parenchyma. Because proteins such as ALBI are expected to have a relatively low distribution in the brain, blood contamination was background-subtracted using a ^{123}I-albumin tracer that was administered just prior to sacrifice in addition to a capillary depletion method that was used to remove ^{125}I-ALBI that was sequestered in the brain microvasculature and not transcytosed into the brain parenchyma.

Overall, systemic PK parameters after a 5 mg/kg dose of ^{125}I-ALBI were in agreement with previous data for ALBI in mice, with a maximum concentration (C_{max}) in plasma of 8.4 µg/g (similar to 30-mg steady state C_{max} in humans), time at maximum (T_{max}) of 16 h, and half-life ($t_{1/2}$) of 25 h. The overall radioactivity measured in the brain after administration of ^{125}I-ALBI was very low (<0.02% ID/g), with an overall exposure ratio (AUC_{0-24} brain/plasma) of 0.00034, which was similar to the albumin control (AUC_{0-24} brain/plasma ratio of 0.00018) and approximately 4 times lower than the transferrin control (brain/plasma ratio of 0.00139). In addition, ALBI did not accumulate in the brain, achieving T_{max} concentrations at 24 h with a noticeable reduction in concentration at 48 h.

Supported By: GlaxoSmithKline

1045-P

Effect of Human Proislet Peptide 2B on β-Cell Function in Subjects with Metformin-Treated Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Study

ELAINE WATKINS, LINDA MORROW, ANDREW KRENTZ, PETER FEIG, LORI UPHAM, JOE REISER, MARCUS HOMPESCH, *Chula Vista, CA, Wilmington, DE*

Human prolslet Peptide (HIP) 2B (HIP2B) stimulates differentiation of pancreatic progenitor cells into new islet structures. In a single center, randomized, double-blind, parallel group, placebo-controlled study the effects of 49 days of treatment with HIP2B were examined in adults with Metformin-treated type 2 diabetes. Subjects received HIP2B 400mg (n=14 mean [+SD]

For author disclosure information, see page A696.

age 53 ± 6 y; BMI 32.8 ± 5.1 kg/m^2) or 600 mg (n=14 age 52 ± 8 y; BMI 32.4 ± 5.2 kg/m^2) or placebo (n=10; age 56 ± 7 y; BMI 31.8 ± 5.3 kg/m^2) in a ratio of 3:3:2 respectively as twice-daily (BID, every 12 h ±1 h) subcutaneous injections. Metabolic evaluations were performed during seven in-house periods. Of 38 subjects who were enrolled 30 completed the study. PK: dose-related increases in C_{max} and AUC were observed for HIP2B with no significant difference between the two doses. Prehaptic insulin secretion rates (pmol/kg/min) Placebo: -60.5 +/- 61.25; HIP2B 400 mg: 60.63 +/- 37.17; 600mg: 55.13 +/- 24.31; pooled HIP2B: 58 +/- 22.13 (p 0.031).

Injection site reactions being the most common AE, were of mild to moderate intensity. No clinically significant changes in clinical laboratory values, vital signs or ECGs were observed. In conclusion, HIP2B was associated with trends towards increased insulin secretion with a statistically increase in pre-hepatic insulin secretion rate from baseline to Day 46 in the pooled HIP2B treatment groups. The results support additional studies of HIP2B in type 2 diabetes.

Supported By: CureDM, Inc.

1046-P

Semaglutide Improves Postprandial Glucose and Lipid Metabolism and Delays First-Hour Gastric Emptying in Subjects with Obesity

JULIE HJERPSTED, MADS BUHL AXELSEN, ASHLEY BROOKS, ANNE FLINT, TRINE KVIST, JOHN BLUNDELL, *Søborg, Denmark, Leeds, United Kingdom*

GLP-1 therapies may delay gastric emptying (GE) and thus influence postprandial glucose (PPG) and lipid (PPL) responses. Semaglutide is a human GLP-1 analog. This double-blind, crossover study investigated the effect of once-weekly s.c. semaglutide (dose-escalated to 1.0 mg) vs. placebo in 30 subjects with obesity and without T2D (mean BMI 33.8 kg/m^2). After each 12-week treatment period, PPG metabolism and GE were assessed following a standardized breakfast, and PPL metabolism following a standardized fat-rich breakfast. After 12 weeks of treatment, fasting concentrations of insulin and C-peptide were higher with semaglutide vs. placebo, while glucose, glucagon, triglycerides (TG) and very low density lipoprotein (VLDL) were lower. After a standardized breakfast, PPG, insulin and C-peptide levels were lower with semaglutide vs. placebo. After a standardized fat-rich breakfast, TG, VLDL and Apo B48 (facilitates lipid absorption in the intestine) levels were lower for semaglutide vs. placebo. No statistical difference between treatments was shown for the overall rate of postprandial GE ($AUC_{0\text{-}5h}$); however, for semaglutide vs. placebo, GE was delayed during the first hour. In conclusion, semaglutide improves fasting and postprandial glucose levels, as well as PPL metabolism, vs. placebo, and delays GE during the first hour.

Table. Fasting and Postprandial Analysis of Glucose and Lipid Metabolism Endpoints after 12 Weeks of Treatment in Subjects With Obesity and Without T2D.

Glucose metabolism endpoints	Fasting values		Postprandial values ($iAUC_{0\text{-}5h}$)		
	ETR	95% CI	ETD	95% CI	Relative difference[a]
Glucose	0.95*	[0.91; 0.98]	−1.34* mmol*h/L	[−2.42; −0.27]	−38.5 %
Insulin	1.45*	[1.20; 1.75]	−921* pmol*h/L	[−1461; −381]	−43.4 %
Glucagon	0.86*	[0.75; 0.98]	−1.65 pg*h/mL	[−24.16; 20.85]	−5.0 %
C-peptide	1.35*	[1.20; 1.52]	−1.42* nmol*h/L	[−2.33; −0.51]	−28.7 %
Lipid metabolism endpoints	**Fasting values**		**Postprandial values ($iAUC_{0\text{-}8h}$)**		
	ETR	95% CI	ETD	95% CI	Relative difference[a]
Triglycerides	0.88*	[0.80; 0.98]	−4.51* mmol*h/L	[−6.15; −2.87]	−40.7 %
VLDL	0.79*	[0.66; 0.95]	−1.17* mmol*h/L	[−2.03; −0.32]	−42.8 %
Apo B48	1.02	[0.86; 1.21]	−0.0455* g*h/L	[−0.0690; −0.0220]	−49.6 %
FFA	0.99	[0.88; 1.11]	0.052 mmol*h/L	[−0.060; 0.163]	15.6 %

ETR: Estimated treatment ratio; Semaglutide/placebo, ETD: Estimated treatment difference; Semaglutide – placebo

[a]Estimated treatment difference/estimated mean for placebo x100%. Apo B48, serum apolipoprotein B48; FFA, free fatty acids; $iAUC_{0\text{-}5h}$, incremental area under the 0–5 hour curve; $iAUC_{0\text{-}8h}$, incremental area under the 0–8 hour curve; VLDL, very low density lipoprotein

*p<0.05

1047-P

Treatment Effectiveness in the 24 Months following Initiation of Exenatide Once Weekly Compared with Basal Insulin for Type 2 Diabetes Patients Naïve to Injectable Therapy in UK Primary Care

QING QIAO, CHRISTOPHER L. MORGAN, SUSAN GRANDY, KRISTINA M. JOHNSSON, SARA JENKINS-JONES, CRAIG J. CURRIE, *Mölndal, Sweden, Cardiff, United Kingdom, Gaithersburg, MD*

Glycaemic and weight change outcomes were compared for type 2 diabetes patients treated with either exenatide QW (Bydureon) or basal insulin. Retrospective data (2010-14) were extracted from the Clinical Practice Research Datalink; a UK primary care database. Patients previously naïve to injectable therapy initiating exenatide QW or basal insulin were matched by propensity score. Absolute and relative change in HbA1c and weight from baseline and the proportion of patients achieving HbA1c <7.0% combined with weight reduction targets of i) any weight loss or ii) ≥5.0% from baseline were compared at 6 months and 12-24 months. 485 patients initiated exenatide QW and 13,503 initiated basal insulin. Patient numbers for each matched analysis are shown in Table 1. HbA1c decreased at 6 and 12-24 months with no significant difference between the cohorts (Table 1). Weight decreased for exenatide QW patients at 6 and 12-24 months but increased in the basal insulin group. The difference in weight change was statistically significant at each time-point (Table 1). A significantly greater proportion of exenatide QW patients met the HbA1c and weight targets at both timepoints. In this real-world data analysis, exenatide QW was associated with equivalence in glycaemic control and greater weight reduction compared with basal insulin.

Table 1. Change in HbA1c and Weight from Baseline and Proportion Achieving Combined Glycemic and Weight Loss Targets for Patients Initiating Therapy with Either Exenatide QW or Basal Insulin.

	6 months			12-24 months		
	Exenatide QW	Basal insulin	p	Exenatide QW	Basal insulin	p
HbA1c (%) change from baseline						
n	206	206		111	111	
Females (n, %)	81 (39.3%)	91 (44.2%)		39 (35.1%)	39 (35.1%)	
Baseline age (Mean years, (sd))	57.7 (11.1)	59.5 (11.8)		57.9 (10)	58.5 (11)	
Baseline HbA1c (Mean , (sd))	9.5 (1.6)	10.1 (1.8)		9.5 (1.7)	9.8 (1.6)	
Mean absolute HbA1c change	-1.33	-1.24	0.450	-1.19	-1.17	0.899
Mean relative HbA1c change	-13.0%	-10.0%	0.899	-11.0%	-9.8%	0.690
Weight (kg) change from baseline						
n	201	201		100	100	
Females (n, (%)	70 (34.8%)	69 (34.3%)		37 (37.0%)	48 (48.0%)	
Baseline age (Mean years, (sd))	56.9 (10.5)	57.1 (12.4)		58.6 (10.2)	59.4 (11.2)	
Baseline weight (Mean, (sd))	110.7 (19.9)	108 (22.2)		108.3 (19.6)	103.1 (20.6)	
Mean absolute change	-3.7	1.2	<0.001	-3.2	2.5	<0.001
Mean relative change	-3.10%	1.20%	<0.001	-2.7%	2.5%	<0.001
Patients reaching target						
n	161	161		88	88	
Females (n, (%)	56 (34.8%)	53 (32.9%)		32 (36.4%)	36 (40.9%)	
Baseline age (Mean years, (sd))	57.2 (10.2)	57.4 (13.1)		57.7 (10.9)	56.3 (12.3)	
Baseline HbA1c (Mean , (sd))	9.4 (1.5)	9.3 (1.8)		9.5 (1.6)	9.5 (1.7)	
Baseline weight (Mean , (sd))	110.7 (19.9)	106.1 (20.2)		107.1 (18.8)	103.5 (18.1)	
HbA1c < 7.0% and any weight loss	36 (22.4%)	16 (9.9%)	0.002	16 (18.2%)	7 (8.0%)	0.044
HbA1c < 7.0% and weight loss ≥ 5%	19 (11.8%)	6 (3.7%)	0.007	7 (8.0%)	0 (0%)	0.007

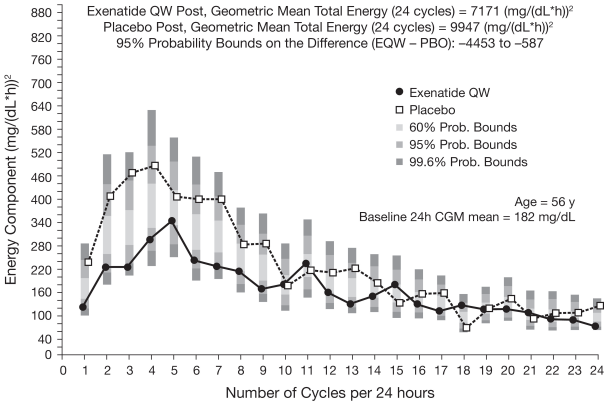
1048-P

Effects of Exenatide Once Weekly on Dynamics of 24 h Glucose Patterns in Patients with T2D

POUL STRANGE, JAMES A. RUGGLES, SERGEY ZHUPLATOV, MICHAEL F. MILLER, *Princeton Junction, NJ, Fort Washington, PA*

Reducing glycemic fluctuations is an important component of glucose control. This randomized, controlled, double-blind, phase 4 clinical study investigated glucose fluctuations with the GLP-1 receptor agonist exenatide QW (EQW) vs. placebo (PBO) using continuous glucose monitoring (CGM). Patients with T2D uncontrolled on background Metformin (MET) were randomized to EQW 2 mg or PBO for 10 wks. Glucose concentration was measured over 7d at lead-in and wks 4 and 10 using CGM (Dexcom G4). In the EQW (N=60)/PBO (N=56) groups, mean baseline age was 55/56 y and A1c was 8.2/8.0%. A measure of glucose fluctuation, distance traveled (arc length of the mean 24 h glucose curve), decreased with EQW compared to PBO (wk 10: –81 mg/dL over 24 h, P=0.004) from a baseline of 755/730 mg/dL over 24 h, and another, total energy (sum of squared frequency times amplitude of Fourier coefficients for the 24 h individual average glucose curves averaged for a week over 24 h) also decreased with EQW compared to PBO [wk 10: –4893 (mg/(dL*h))^2 over 24 h, P=0.003] from a baseline of 12341/9953 (mg/(dL*h))^2 over 24 h. Energy spectrum analysis showed the reduction was confined to slower glucose changes rather than fast changes (Figure) and indicated substantial differences depending on mean glucose and age (not shown). Thus EQW significantly reduced measures of glucose fluctuation, such as distance traveled and energy, compared with PBO. (NCT02288273).

Figure. Energy Spectrum Analysis.



Supported By: AstraZeneca (NCT02288273)

ADA-Supported Research Moderated Poster Discussion

For author disclosure information, see page A696.

1049-P

Long-Acting GLP-1 and Glucagon Receptor Dual Agonists for the Treatment of Type 2 Diabetes

SEOHEE YOU, MARY MCDONALD, MARTIN CASE, DEREK STEINER, TIMOTHY TAT, CELIA JENKINSON, REBECCA PICK, JULIET HART, VERONICA MORENO, JASON PARISE, WEN YAN, RAUL CAMACHO, RONALD SWANSON, ELLEN CHI, KEITH DEMAREST, JAMES LEONARD, *Spring House, PA, San Diego, CA*

Obesity is a major contributing factor to type 2 diabetes, the prevalence of which is increasing worldwide. Oxyntomodulin (OXM) is a gut peptide with short half-life, that is a balanced agonist at both GLP-1 and glucagon receptors. Dual GLP-1R/GCGR agonists have been shown not only to improve glycemic control via GLP-1R, but also induce profound weight loss through dual agonism in mice. Extending the circulating half-life of dual GLP-1R/GCGR agonists is a required pharmaceutical attribute. PEGylation is a commonly used strategy to extend the half-life of peptides, but conjugation often results in reduced potency. We addressed this challenge by employing a "cysteine scan" of OXM to investigate optimal sites of conjugation. Additionally, conjugation was performed with a bifunctional 30 kDa PEG to generate peptide homodimers, with the objective of achieving synergistic gains in potency through increased avidity. Conjugation of K30C OXM to PEG yielded an OXM-PEG homodimer that was close in potency to native OXM at both GLP-1R and GCGR. Substitution of amino-isobutyrate at position 2, in combination with truncation of residues 32-37, produced a protease resistant PEGylated agonist (JNJ-54728518) with good potency at both receptors. The half-life of JNJ-54728518 was 18 hours in lean mice. Diet-induced obese (DIO) mice dosed with JNJ-54728518 significantly improved glucose tolerance in association with increased glucose-dependent insulin secretion. The metabolic effects of JNJ-54728518 were also assessed by repeat dosing in DIO mice. JNJ-54728518 (10 nmol/kg) showed superior efficacy compared with liraglutide (10 nmol/kg) in glucose lowering (59 vs. 118 mg/dL), reduction of daily food intake (0.04 vs. 0.07 g/g body weight), fat loss (12.3 vs. 6.0 g), and body weight loss (-26.91 vs. -7.44%). JNJ-54728518 at all doses markedly reduced cholesterol levels, whereas liraglutide had no significant effect. Thus, JNJ-54728518 had a well-differentiated efficacy profile vs. liraglutide in DIO mice.

1050-P

Neurturin Prevents Development of Hyperglycemia and Reduction in β-Cell Mass in Zucker Diabetic Fatty Rats

JAMES L. TREVASKIS, HANI JOUIHAN, STEPHANIE OLDHAM, SAFINA ALI, JENNIFER CANN, YUAN CHANG, TERRENCE O'DAY, CHRISTINA REERS, MARIA SORHEDE WINZELL, DAVID M. SMITH, UWE ANDAG, LUTZ JERMUTUS, MATTHEW COGHLAN, JOSEPH GRIMSBY, CORD DOHRMANN, CRISTINA RONDINONE, ARUN SHARMA, *Gaithersburg, MD, Gottingen, Germany, Mölndal, Sweden, Cambridge, United Kingdom*

Screening of embryonic pancreatic cDNA library for secreted proteins resulted in the identification of a neurotrophic factor neurturin (NRTN). Here, we examined the role of NRTN, a member of the glial-derived neurotrophic factor family that regulates formation of peripheral nerves, in regulating glycemic control. We administered recombinant human NRTN to 8 week old male Zucker diabetic fatty (ZDF) rats (at 1, 3 and 10 mg/kg/d) for 29 days and compared the effects on body weight, glucose and metabolic parameters to ZDF rats administered vehicle or the glucagon-like peptide-1 receptor agonist liraglutide (0.4 mg/kg/d). NRTN dose-dependently prevented the rapid development of hyerglycemia. Whereas glucose (in mg/dL) increased in vehicle group (213 ± 31) over the treatment period, NRTN at doses of 3 mg/kg (92 ± 38) and 10 mg/kg (-16 ± 19) abrogated this increase similar to effect of liraglutide (-7 ± 7, all $p<0.001$ vs. vehicle). Glycated hemoglobin (%HbA1c) levels were lower in liraglutide (3.3%) and 3 and 10 mg/kg NRTN groups (3.9% and 3.7%) relative to vehicle (7.3%, $p<0.01$). NRTN and liraglutide treatment also reduced plasma lipids and liver enzyme levels. Importantly, unlike liraglutide-treated rats, improvements in metabolism with NRTN were evident in the absence of any change in body weight or food intake. Histological analyses of pancreas showed improved islet architecture and significantly higher β-cell mass in NRTN-treated rats and unchanged β-cell proliferation. Additionally, while pancreatic mass did not change with treatment, insulin content increased dose-dependently with NRTN (1.9-, 2.5- and 4.3-fold vs. vehicle, $p<0.001$ for highest dose), and liraglutide (2.6-fold, $p<0.05$) administration. Our results demonstrate that NRTN prevents development of hyperglycemia, replenishes β-cell insulin content, and reduces both the deterioration of islet architecture and reduction in β-cell mass observed in ZDF rats.

1051-P

Protective Effect of Exenatide against the Development of Diabetes in Prediabetes Subjects

YEOREE YANG, JOONYUB LEE, BORAMI KANG, HAE KYUNG YANG, EUN YOUNG LEE, SEUNG-HWAN LEE, KUN-HO YOON, BONG-YUN CHA, JAE-HYOUNG CHO, *Seoul, Republic of Korea*

Various researches have been conducted to delay or prevent the development of diabetes in prediabetes subjects. We hypothesized that weight reduction and β-cell protective effect of GLP-1 receptor agonist might have preventive effect. In this study, we aimed to investigate the effect of GLP-1 agonist on prediabetes to evolve to overt diabetes. In this retrospective cohort study, we selected the prediabetes subjects who received the exenatide therapy more than 3 months between 2011 and 2013. Subjects who had follow-up visits at least 2-year duration were included. Twofold numbers of prediabetes subjects who visited the outpatient clinic around the same time and received only the life style modification education were selected as a control group. The age, sex, BMI, HbA1c and FPG were matched with exenatide group. Reviewing their medical records, the diagnosis of prediabetes and diabetes was conducted according to the 2015 criteria of the American Diabetes Association. In this period, a total of 20 prediabetes subjects (3 men and 17 women) received exenatide therapy. Baseline mean age, BMI, HbA1c, and FPG were 54.8 ± 9.2 years, 27.7 ± 3.5 kg/m^2, 5.8 ± 0.4% and 109.6 ± 12.5 mg/dL, respectively. Average duration of Exenatide use was 8.7 ± 5.8 months. During the mean follow-up period of 39.3 ± 1.0 months, only 2 new cases (10%) of diabetes were identified in exenatide group compared with 13 new cases (32.5%) in control group. An analysis using the Cox proportional hazards model showed that the risk of developing diabetes increased with higher HbA1c (≥ 6.1%) compared with lower HbA1c (< 6.1%); the relative risks (RR) of diabetes were 6.9 times greater. Owing to the lack of the case number, we could not show the statistical significance. But the Exenatide showed the possibility of risk reduction (RR 0.33, 0.95% confidence interval (CI) 0.068 to 1.597, p=0.168). in conlusion, exenatide showed the possibility of prevention of diabetes. Further large scale prospective randomized controlled study is needed.

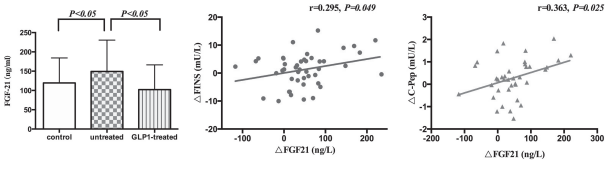
1052-P

Exenatide Treatment Decreases the Circulating FGF-21 in Patients with Newly Diagnosed Type 2 Diabetes

YANJIN HU, JIA LIU, YUAN XU, GUANG WANG, *Beijing, China*

Fibroblast growth factor 21 (FGF-21) has been demonstrated as a metabolic regulator with multiple beneficial effects. Studies have shown that type 2 diabetes (T2D) patients had increased FGF-21 levels and decreased expression of the FGF receptors, which suggested an "FGF-21-resistance" state. The aim of this study was to investigate the effects of the glucagon-like peptide-1 receptor agonist (exenatide) on the FGF-21 in newly diagnosed T2D patients. 102 participants including 47 newly diagnosed T2D patients and 55 healthy controls were recruited. T2D patients were assigned to 12 weeks of exenatide treatment. The FGF-21 levels and other metabolic parameters were measured before and after exenatide treatment. The results showed that T2D patients had significantly higher FGF-21 levels than the controls. In T2D patients, exenatide treatment resulted in a significant decrease in BMI, HbA1c, HOMA-IR and FGF-21 while HOMA-B was significantly higher after treatment. The decrease in FGF-21 (ΔFGF-21) was positively correlated with increased fasting insulin (ΔFINS) and C peptide (ΔC-Pep) levels. The FGF-21 levels in newly diagnosed T2D patients are increased. Exenatide treatment lowered plasma FGF-21 levels with the recovery of insulin secretion (Figure 1). The FGF-21 of newly diagnosed T2D patients before and after exenatide treatment and controls and correlation between ΔFGF-21 and ΔFINS and ΔC-Pep.

Figure 1.



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For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

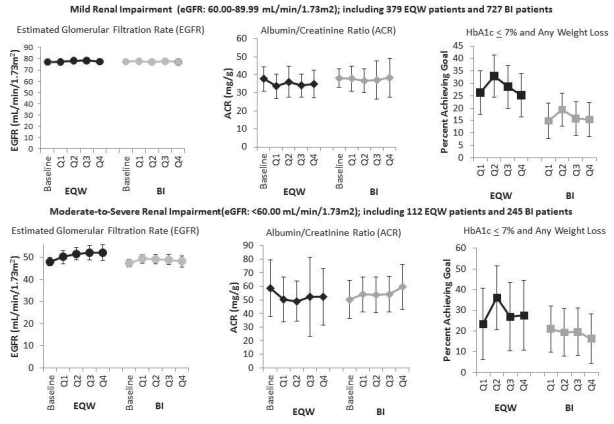
1053-P

Real-World Use of Exenatide Once-Weekly Compared with Basal Insulin among Type 2 Diabetic Patients with Renal Impairment

ANITA M. LOUGHLIN, QING QIAO, KRISTINA M. JOHNSSON, SUSAN GRANDY, STEPHEN EZZY, LAURA YOCHUM, C. ROBIN CLIFFORD, ROBERT GATELY, ANTHONY P. NUNES, DAVID D. DORE, JOHN D. SEEGER, *Waltham, MA, Mölndal, Sweden, Gaithersburg, MD*

Little is known about the risks and benefits of using of renally-excreted exenatide once-weekly (EQW) instead of basal insulin (BI) in patients with type 2 diabetes (T2D). From a large U.S. electronic health record database, between 2012 and 2015, we enrolled injectable-naïve EQW or BI initiators in a propensity score matched cohort study of T2D patients. Cohort subsets with mild and moderate-to-severe renal impairment (RI) were examined. Measures of eGFR, albumin/creatinine ratio, HbA1c and weight were identified at baseline and quarterly in the first year of follow-up. Gastrointestinal (GI) symptoms were identified by diagnostic codes, and hypoglycemia by diagnostic codes and clinical notes. Renal function remained stable in all RI cohorts (Figure). EQW users, regardless of renal function, were more likely to achieve HbA1c ≤ 7% with weight loss relative to BI users (Figure). Nausea and vomiting occurred more frequently in EQW vs. BI patients, RR (95% CI): 1.28 (0.84, 1.95) within mild RI cohort and 1.59 (0.85, 2.69) within moderate-to-severe RI cohort. Hypoglycemia occurred less often in EQW patients relative to BI patients, RR (95% CI): 0.92 (0.61, 1.41) within mild RI cohort and 0.62 (0.33, 1.19) within moderate-to-severe RI cohort. In T2D patients with RI, risks of using EQW instead of BI include more GI symptoms; benefits include less hypoglycemia and more glycemic control with weight loss.

Figure. Renal Function and Glucose Control with Weight Loss in Exenatide Once-weekly (EQW) or Basal Insulin (BI) Initiators with Renal Impairment, at Initiation (Baseline) and Quarterly (Q1-Q4) During the First Year of Follow-up (Mean and 95% Confidence Intervals).



Supported By: AstraZeneca

1054-P

Early Lixisenatide Treatment Improves β-cell Function in Patients with Type 2 Diabetes

YOSHINOBU KONDO, SHINOBU SATOH, YASUO TERAUCHI, *Kanagawa, Japan*

Preclinical studies with lixisenatide have suggested improvements in β-cell function. Therefore, we investigated these effects using the glucagon stimulation test (GST). Forty-seven patients with type 2 diabetes were introduced lixisenatide and their β-cell function was measured with 1 mg intravenous GST at weeks 0 and 24. Lixisenatide was initiated at 10 μg/day and titrated up to 20 μg/day. Its effect on β-cell function was assessed by the change in the area under the curve (AUC) of serum C-peptide immunoreactivity (CPR) during GST (AUC-CPR = (sum of CPR levels before and 6 min after GST) x 6 min/2). In full-set analysis, AUC-CPR increased after 24 weeks of lixisenatide treatment (7.95 ± 1.14 ng/ml·min to 9.71 ± 0.96 ng/ml·min, p = 0.005). In univariate regression model analysis, a negative relation was seen between change in AUC-CPR (ΔAUC-CPR = (AUC-CPR at week 24) – (AUC-CPR at week 0)) and diabetes duration (duration: β = –0.26, 95% confidence interval (CI) –0.40 to –0.11, p < 0.001, R^2 = 0.23). In multivariate regression model analysis, the effect of diabetes duration on ΔAUC-CPR was confirmed even after adjustments for potential confounders (duration: β = –0.18, 95% CI –0.30 to –0.05, p = 0.007, R^2 = 0.59). In tertile analysis by duration of diabetes, early lixisenatide treatment significantly improved AUC-CPR (duration ≤ 6 years: +2.65 ± 1.52 ng/ml·min, p = 0.004; duration 7 to 16 years: +3.54 ± 1.22 ng/ml·min, p = 0.003), whereas late lixisenatide treatment (duration > 16 years) did not (-1.61 ± 1.46 ng/ml·min, p = 0.46). In receiver operating characteristic (ROC) analysis, the cut-off value for treatment duration for positive lixisenatide effect on ΔAUC-CPR was 7 years (area under the ROC curve 0.70, sensitivity 88% and specificity 47%). These findings suggest that early lixisenatide treatment potentially improves β-cell function in patients with type 2 diabetes.

1055-P

PF-05231023, a Long-Acting FGF-21 Analog, Increases Blood Pressure and Induces Compensatory Diuresis and Thirst in Rats

MYLENE PERREAULT, TOD TURNER, SHERRY CHIN, XIAN CHEN, LISA BRIDEAU, DOMINICA LOPES, GEORGE J. DEMARCO, BRYAN GOODWIN, *Cambridge, MA*

Fibroblast growth factor-21 (FGF-21) is a hormone secreted by the liver in response to starvation. In addition to its well-characterized effects on insulin sensitivity in rodents, FGF-21 has been shown to increase water intake in mice. In this study, we sought to determine the mechanism by which FGF-21 increases water intake in rodents. Eight week-old Wistar Han rats received a single dose of PF-05231023 before they were placed in metabolic cages for determination of water intake and urine output. PF-05231023 significantly increased water consumption in rats, which was accompanied by a concomitant increase in urine output. Interestingly, the effect of PF-05231023 on urine output appeared prior to a significant change in water intake. PF-05231023-treated rats excreted more electrolytes (Na, K, Cl) than control animals but were able to normally regulate urine output and excretion of electrolytes in response to water deprivation. Furthermore, the sodium balance in PF-05231023-treated animals was normal and plasma renin activity, vasopressin and atrial natriuretic peptide levels were unchanged, suggesting that PF-05231023 may be regulating diuresis by an indirect mechanism. Increased urinary output represents a compensatory mechanism involved in the long-term regulation of blood pressure, so we next examined the effects of PF-05231023 in telemeter-implanted rats. PF-05231023 rapidly and significantly increased mean arterial blood pressure with associated increase in urine output. Altogether, our data suggests that PF-05231023 initially raises blood pressure, which leads to a compensatory increase in diuresis followed by a compensatory increase in water intake.

1056-P

Real-World Clinical Outcomes among Exenatide Once-Weekly Initiators Compared with Matched Initiators of Basal Insulin

ANITA M. LOUGHLIN, QING QIAO, KRISTINA M. JOHNSSON, SUSAN GRANDY, STEPHEN EZZY, LAURA YOCHUM, C. ROBIN CLIFFORD, ROBERT GATELY, ANTHONY P. NUNES, DAVID D. DORE, JOHN D. SEEGER, *Waltham, MA, Mölndal, Sweden, Gaithersburg, MD*

This propensity-matched retrospective cohort study included injectable-naïve patients with type 2 diabetes who initiated exenatide once-weekly (EQW) or long-acting basal insulin (BI) between 2012 and 2015 within a large U.S. electronic health record database. Body weight and hemoglobin A1c (HbA1c), assessed at baseline and quarterly during the first year of follow-up, were summarized as the mean of observed or multiply-imputed values within each quarter. We identified hypoglycemia using diagnostic codes and natural language processing of clinical notes. The EQW (N=1,005) and BI (N=1,944) cohorts had comparable characteristics at baseline (mean weight and HbA1c: EQW, 109.2 kg and 8.2%; BI, 107.8 kg and 8.4%). The EQW cohort lost 1.03 kg of body weight on average, in the first quarter after initiation, and lost 2.15 kg by the end of the year. No appreciable average weight change was observed in the BI cohort, with 0.03 kg lost in the first quarter, and a 0.09 kg weight gain by end of first year. In the first quarter after initiation, average HbA1c declined 0.45 percentage points (95% CI: 0.4, 0.5) in the EQW cohort and 0.27 percentage points (95% CI: 0.2, 0.3) in the BI cohort. The greatest declines in HbA1c occurred in the second quarter; a 0.66 and 0.48 percentage point decline in EQW and BI cohorts, respectively, with little further change in the first year. The percentage of the EQW cohort who achieved both glycemic control (HbA1c ≤ 7%) and any weight loss was greater than in the BI cohort; the peak difference occurred in the second quarter: EQW, 29.7% (95% CI: 24.3%, 35.1%) and BI, 16.9% (95% CI: 12.6%, 21.2%). The incidence of hypoglycemia per 1,000 person-years was 9.2 (95% CI: 38.9, 61.3) in the EQW cohort, and 59.7 (95% CI: 51.4, 68.9) in the BI cohort. EQW offers a clinical advantage compared to BI with respect to likelihood of achieving both glycemic control and weight loss, along with a lower incidence of hypoglycemia.

Supported By: AstraZeneca

1057-P

Injectable GLP-1 Receptor Agonists Have a Significant Placebo Effect on Weight and Adverse Symptoms: A Systematic Review and Meta-analysis

HELENA M. DE WIT, MAARTEN TE GROEN, MAROESKA M. ROVERS, CEES J. TACK, *Nijmegen, Netherlands*

Background: Whether treatments for type 2 diabetes (T2DM) and their route of administration include placebo effects is completely unknown. We reasoned that therapy with injectable GLP-1 receptor agonists (GLP-1ra), generates placebo effects on weight, glucose control (A1c) and adverse symptoms. To test this hypothesis, we compared injectable placebo GLP-1ra with oral placebo DPP-4 inhibitor (DPP-4i) and placebo SGLT2 inhibitor (SGLT2i) treatment.

Methods: PubMed, EMBASE, and Central were searched for randomized placebo-controlled trials investigating GLP-1ra, DPP-4i or SGLT2i. Data on placebo groups were extracted and pooled using a generic inverse variance random effects model.

Results: 67 trials were included, involving 2522, 5290, and 2028 patients randomized to placebo GLP-1ra, placebo DPP-4i, and placebo SGLT2i, resp. Body weight decreased significantly with placebo GLP-1ra (placebo short-acting GLP-1ra: 0, 76 kg [95% CI -1.10, -0.43], no significant changes occurred with placebo DPP-4i (-0.31kg [-0.64, +0.01]. Weight loss with placebo showed a strong correlation with the active comparator drug (R^2=0.40-0.78). Placebo treatment had little effect on A1c (-0.23%, 0.10%, and -0.13% for placebo GLP-1ra, DPP-4i, and SGLT2i, resp.). Adverse events occurred frequently with placebo, were strongly associated with the adverse effects of the active comparator drug, and led to drop-out in 2.0-2.7% of cases.

Conclusion: Injectable GLP-1 ra's have a significant placebo effect on weight and adverse symptoms. Interestingly, the efficacy of placebo treatment was related to the efficacy of the active comparator, and the side effect profile induced by placebo was related to the side effects of the comparator drug. Altogether, our results suggest that subjective expectations affect T2DM treatment efficacy and side effects, an observation that could be employed therapeutically.

1058-P

Effect of Liraglutide on Fat Distribution in Type 1 Diabetes

MARIE-CHRISTINE DUBE, MARTIN D'AMOURS, S. JOHN WEISNAGEL, *Quebec City, QC, Canada*

Overweight is present in type 2 and also in type 1 diabetes. The effect of liraglutide is relatively unknown in overweight patients with type 1 diabetes and even less is documented regarding the specific anthropometric components. We investigated the effect of 24 weeks of treatment with liraglutide combined with basal/bolus insulin regimen on fat distribution in overweight subjects with type 1 diabetes.

In a double-blind fashion, patients (n = 15) were assigned to insulin + placebo or insulin + liraglutide for 24 weeks. Measures of fat distribution (waist and hip circumferences, skinfold thickness, percentage of body fatness, abdominal and mid-thigh computed tomography scans) were obtained in 15 overweight patients under baseline, liraglutide and placebo conditions. Other metabolic parameters were also measured. Paired *t* tests were used to compare the changes in the variables of interest.

With liraglutide, all markers of fat distribution decreased clinically and significantly. BMI decreased from 30.5 ± 0.9 to 28.5 ± 1.0 kg/m^2 ($p < 0.001$), waist and hip circumferences each decreased by about 3 cm ($p < 0.05$). The sum of skinfold thickness decreased from 220 ± 45 to 176 ± 12 mm ($p < 0.0001$). Percentage of body fat went from 33.2 ± 1.6 to 31.3 ± 1.8% ($p < 0.05$). Total and subcutaneous adipose tissue decreased significantly ($p < 0.0005$), decrease in visceral adipose tissue was of bordeline significance ($p = 0.057$). With liraglutide, changes in VAT from baseline were correlated with changes in insulin sensitivity. Daily total and bolus insulin doses fell from 70.9 ± 10.9 to 66.7 ± 11.9 units ($p < 0.05$) and from 39.3 ± 5.8 to 34.6 ± 5.4 units ($p < 0.01$), respectively.

The addition of liraglutide to basal/bolus insulin therapy for 24 weeks in overweight type 1 diabetes individuals significantly improved fat distribution and related metabolic parameters. Longer term studies evaluating clinical endpoints will be required to further document the role of GLP-1 agonist therapy on obesity and fat distribution in type 1 diabetes.

Supported By: Novo Nordisk Inc.

1059-P

Sparse-Matrix Sampling of Antifibrillation Sequence Mutations Yields a Library of Novel Solution Stable Glucagon Analogs Suitable for an Artificial Pancreas

YANYU PENG, STEPHEN EISENBERG, LIZ SCHANUEL, ALEXANDER KISLUKHIN, MISHA PLAM, MICHAEL STOWELL, *Boulder, CO*

Glucagon is commonly used to treat severe episodes of hypoglycemia diabetics and is a required hormone for a fully functional artificial pancreas. However, native glucagon has physicochemical properties that prevent solution formulation primarily due to fibrillation. Attempts to mitigate the fibrillation properties of glucagon have been varied and fall into two general classes; formulation strategies and sequence modifications to enhance solubility at physiological pH. These strategies have been met with modest success and to date there are no solution stable glucagon analogues or formulations approved by the FDA. Here we describe the implementation of a sparse matrix sampling of anti-fibrillation mutations to discover novel solution stable glucagon analogues. All of the analogues demonstrate superior solution stability at physiological pH. Surprisingly, some of the most solution stable analogues have only a modest isoelectric point shift in contraindication to the expected solubility requirement at physiological pH. Several of the analogues were tested for glucagon receptor activation and found to have activities ranging from 60% to 90% of native glucagon. In conclusion, application of a spare matrix sampling method allowed discovery of novel solution stable glucagon analogues with unexpected properties and activities suitable for implementation in an artificial pancreas.

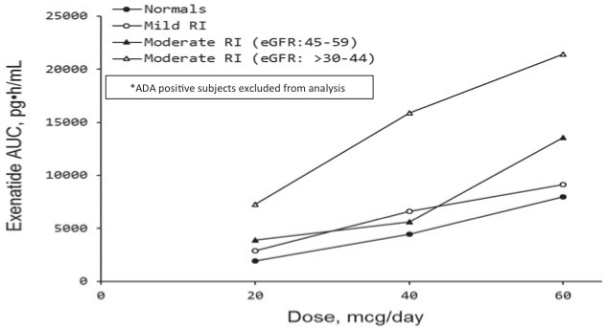
1060-P

Effects of Renal Impairment on the Pharmacokinetics of ITCA 650

LISE KJEMS, MAYA PELTZ, ROBERT FIELDING, HOLLY HUANG, MICHELLE A. BARON, *Boston, MA, Boulder, CO*

The PK, safety and tolerability of ITCA 650, a subdermally placed osmotic mini-pump that delivers continuous SC exenatide (EX) for extended periods of time, was studied in subjects with varying degrees of renal impairment (RI). Escalating doses of ITCA 650 20, 40 and 60 mcg/day were placed for consecutive periods of up to 20 days each in 37 subjects (mean age, 57), stratified by eGFR (mL/min/1.73 m^2) into: normal (≥90), mild RI (60-89), moderate RI (45-59) and moderate RI (>30-44). The primary endpoint was steady state plasma AUC for each dose, derived from 7 time points over 24 hours. Safety and antidrug antibodies [ADA] were monitored. EX AUC increased 2.6-3.7 fold, and clearance decreased 1.1-3 fold with increasing RI as previously reported for exenatide. Steady state AUC and EX concentrations (Css) increased 3 to 4-fold over the dose range studied. ITCA 650 was well tolerated. The most common AE was nausea. There were no renal SAEs or study drug-related renal AEs. EX AUC and Css rose with dose and with increased renal impairment. The overall safety and GI tolerability of ITCA 650 in mild and moderate renal impaired subjects were consistent with previous studies involving ITCA 650.

Figure. Renally-Impaired Patients.*



Supported By: Intarcia Therapeutics, Inc.

1061-P

Analysis of Absorption and Excretion Route of Efpeglenatide Using Radiolabeled [^{125}I-CA-Ex4] Efpeglenatide, [^{125}I-Ig4 Fc] Efpeglenatide and [^{14}C-PEG] Efpeglenatide

YOUNG MI LEE, TAE HUN SONG, CHANG KI LIM, DAE JIN KIM, KYUNG JIN CHOI, SE CHANG KWON, *Hwaseong, Republic of Korea*

Efpeglenatide is composed of *CA*-Exendin-4 chemically conjugated to recombinant human immunoglobulin G4 Fc fragment through a non-peptidyl linker. Efpeglenatide has an extended pharmacokinetic (PK) profile with prolonged pharmacodynamic (PD) action through its unique LAPSCOVERY con-

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

jugation and through CA Exnedine-4's hypothesized super-agonistic pharmacologic properties on the GLP-1 receptor. The absorption and the excretion profiles of efpeglenatide were evaluated in a rat model following intravenous (IV) or subcutaneous (SC) administration of radiolabeled efpeglenatide at the dose of 24 nmoles/kg. Efpeglenatide was labeled on three different positions: [^{125}I]-radiolabeling on *CA*-Exendin-4 and Ig4 Fc fragment, and [^{14}C]-radiolabeling on the non-peptide linker PEG. The level of radioactivity in serum and excreta was determined based on liquid scintillation counting or gamma counting methods. The bioavailability (BA) was in the range from 81 to 88% and long terminal elimination half-lives (47~56h) were the most pronounced PK characteristics of radiolabeled efpeglenatide. Following both IV and SC administration of efpeglenatide labeled on [^{125}I]-*CA*-Exendin-4 and on [^{125}I]-Ig4 Fc, the excretion profiles were qualitatively similar with a fast initial elimination up to 7 to 9 days and a subsequent slower process until the end of study. The major route of elimination was via the kidneys (78-84%) with a total recovery of radioactivity at Day 21 of 96-99%. The amount of dose eliminated via feces after [^{14}C]-Epeglenatide administration was slightly higher than [^{125}I]-Epeglenatide (18% vs. 7-10%). In conclusion, radioactivity of [^{125}I]-and [^{14}C]-Efpeglenatide exhibited similar absorption profiles with BA (81 ~ 88%) and showed long terminal half-lives, and the urinary excretion was the major route of elimination.

1062-P

Insulin Glargine/Lixisenatide Fixed-Ratio Combination Outcomes Are Similar for North American and Rest of World T2D Populations

GEORGE DAILEY, TIMOTHY S. BAILEY, HARPREET S. BAJAJ, TERRY DEX, MELANIE GROLEAU, WILLIAM STAGER, AARON VINIK, *La Jolla, CA, Escondido, CA, Brampton, ON, Canada, Bridgewater, NJ, Laval, QC, Canada, Norfolk, VA*

LixiLan is a once-daily titratable, single injection, fixed-ratio combination of insulin glargine 100 U/mL (Gla-100) and lixisenatide in development for treating T2D. We compared clinical and safety outcomes for patients (pts) in the LixiLan-O and -L phase 3 clinical trials from sites in North America (NA; U.S. and Canada) and rest of the world (RoW).

LixiLan was compared over 30 weeks with Gla-100 and lixisenatide in pts uncontrolled on Metformin ± oral antidiabetes drugs (OADs) (LixiLan-O); and with Gla-100 in pts uncontrolled on basal insulin ± OADs (LixiLan-L).

Compared to Gla-100 or lixisenatide alone, LixiLan improved glycemic outcomes (A1c, postprandial plasma glucose change, achievement of A1c < 7.0% and composite endpoint [A1c < 7.0% with no hypoglycemia or weight gain)], which were generally comparable across NA and RoW pts. Gastrointestinal (GI) adverse events (AEs) for LixiLan were numerically higher vs. Gla-100, but numerically lower vs. lixisenatide, with no statistical differences between NA and RoW pts ($P > 0.05$, Table). No differences in documented hypoglycemia were seen between NA and RoW. NA pts experienced weight neutrality (LixiLan-O) to weight loss (LixiLan-L); RoW pts lost weight with LixiLan in both trials.

LixiLan consistently improved glycemic parameters, with no differences in hypoglycemia risk and GI AEs between pts in NA and RoW across both trials.

Table. Patient Characteristics and Efficacy/Safety Outcomes for NA and RoW Populations.

	LixiLan			Gla-100			Lixisenatide		
LixiLan - O[a]	**NA (N = 136)**	**RoW (N = 333)**	***P* Value**	**NA (N = 156)**	**RoW (N = 311)**	***P* value**	**NA (N = 80)**	**RoW (N = 153)**	***P* value**
A1c, %									
Baseline	8.19 (0.69)	8.03 (0.71)	0.031	8.22 (0.71)	8.01 (0.67)	0.002	8.34 (0.78)	8.02 (0.67)	0.001
Week 30	6.65 (0.87)	6.50 (0.74)	0.052	6.99 (0.78)	6.76 (0.77)	0.002	7.64 (0.88)	7.18 (0.85)	< 0.001
Change from baseline	−1.53 (0.91)	−1.53 (0.87)	0.995	−1.22 (0.85)	−1.24 (0.88)	0.805	−0.70 (0.89)	−0.84 (0.86)	0.221
A1c < 7.0% at endpoint, %	66.9	76.5	0.039	52.9	62.7	0.044	17.5	41.2	< 0.001
PPG[b], mg/dL									
Baseline	263.1 (66.8)	277.7 (64.5)	0.040	250.1 (58.9)	269.0 (67.6)	0.005	261.8 (55.7)	266.8 (61.8)	0.584
Change from baseline	−116.2 (79.3)	−106.3 (76)	0.237	−60.7 (61.8)	−58.0 (64.7)	0.690	−92.9 (71.0)	−86.3 (75.7)	0.753
Weight, kg									
Baseline	91.8 (18.0)	88.5 (16.8)	0.055	89.8 (16.8)	89.7 (16.2)	0.944	89.5 (18.2)	91.5 (15.2)	0.378
Change from baseline	0.3 (4.2)	−0.5 (3.4)	0.034	1.8 (4.1)	0.8 (4.1)	0.008	−1.5 (3.2)	−2.7 (3.4)	0.006
Documented hypoglycemia[c], %	21.3	27.3	0.160	22.4	24.1	0.684	5.0	7.2	0.495
Nausea, %	9.6	9.6	0.986	7.1	1.9	0.020	33.8	19.0	0.016
Vomiting, %	5.1	2.4	0.185	2.6	1.0	0.247	11.3	3.9	0.058
Proportion of pts with A1C < 7.0%, no weight change and no documented hypoglycemia at endpoint, %	25.7	34.3	0.060	11.0	22.8	0.001	13.8	32.7	< 0.001
LixiLan-L[d]	**N = 105**	**N = 262**		**N = 91**	**N = 274**				
A1c, %									
Baseline	8.12 (0.71)	8.05 (0.67)	0.319	8.12 (0.73)	8.06 (0.73)	0.521			
Week 30	7.05 (0.94)	6.95 (0.87)	0.330	7.55 (0.87)	7.47 (0.92)	0.478			
Change from baseline	−1.08 (1.01)	−1.10 (0.84)	0.836	−0.57 (0.84)	−0.59 (0.87)	0.840			
A1c < 7.0% at endpoint, %	46.7	58.4	0.041	28.6	29.9	0.805			
PPG[b], mg/dL						<			
Baseline,	248.3 (59.3)	274.4 (70.6)	0.002	244.9 (71.5)	277.5 (62.5)	0.001			
Change from baseline	-81.1 (81.3)	-91.9 (80.7)	0.286	-19.6 (93.3)	-30.6 (69.4)	0.254			
Weight, kg									
Baseline,	87.6 (14.0)	87.9 (14.6)	0.832	89.7 (16.1)	86.2 (14.2)	0.053			
Change from baseline	-0.4 (3.8)	-0.6 (3.0)	0.710	1.2 (2.9)	0.7 (2.7)	0.192			
Documented hypoglycemia[c], %	41.3	39.5	0.741	45.1	41.6	0.566			
Nausea, %	13.5	9.2	0.261	1.1	0.4	0.524			
Vomiting, %	5.8	2.7	0.216	0.0	0.7	0.156			
Proportion of pts with A1c < 7.0%, no weight change and no documented hypoglycemia at endpoint, %	13.3	22.6	0.028	9.9	8.8	0.751			

Data are mean (SD). NA vs. ROW comparisons include all pts with baseline and on-study (LOCF) assessments for A1c, PPG and weight using two sample t-tests and all pts with follow-up assessments for response and adverse event rates using chi-square tests. [a]Pts on Metformin. [b]Measured 2 hours after a standard liquid meal in a subset of pts. [c]Hypoglycemia was defined as: pt displaying symptoms and blood glucose ≤ 70mg/dL or symptoms and response to oral glucose solution. [d]Pts on ± Metformin. PPG, postprandial plasma glucose; SD, standard deviation.

Supported By: Sanofi U.S.

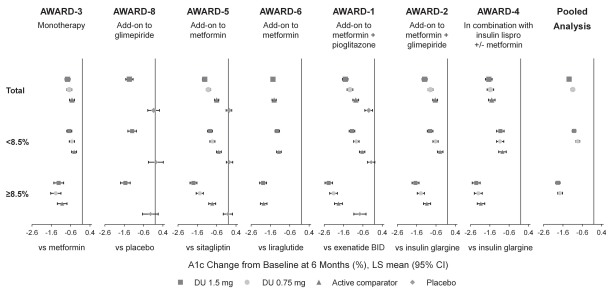
1063-P

Efficacy and Safety by Baseline A1c with Once-Weekly Dulaglutide in AWARD Program

SAMUEL DAGOGO-JACK, VIVIAN THIEU, MARIA YU, NAN ZHANG, DARA SCHUSTER, LUIS-EMILIO GARCIA-PEREZ, *Memphis, TN, Indianapolis, IN, Toronto, ON, Canada*

Dulaglutide (DU), a once weekly GLP-1 receptor agonist, was studied in the AWARD clinical trial program in adult patients (pts) with T2D and demonstrated significant A1c reduction and potential for weight loss. To evaluate the efficacy and safety of DU 1.5 mg and DU 0.75 mg in T2D pts by baseline A1c <8.5% or ≥8.5%, we conducted a *post-hoc* analysis on AWARD-1 to 6 and 8 at 6 months. Across 7 studies, 55 to 82% of the DU-treated pts had a baseline A1c <8.5% and 18 to 45% had a baseline A1c ≥8.5%. The ranges of A1c reductions with baseline A1c <8.5% and ≥8.5%, respectively, were: DU 1.5 mg: -0.67 to -1.25% and -1.22 to -2.37%; DU 0.75 mg: -0.53 to -1.07% and -1.37 to -2.19%. The A1c reduction from the pooled analysis was greater in pts with baseline A1c ≥8.5% than pts with baseline A1c <8.5%, respectively: DU 1.5 mg: -1.86% and -1.02%; DU 0.75 mg: -1.75% and -0.83% (Figure). DU treatments were well tolerated among baseline A1c subgroups. Across the AWARD program, DU 1.5 mg and DU 0.75 mg demonstrated significant A1c reduction in both subgroups with an acceptable safety profile. Compared to pts with baseline A1c <8.5%, pts with baseline A1c ≥8.5% had greater A1c reduction.

Figure.



Supported By: Eli Lilly and Company

1064-P

Effectiveness and Safety of Weekly Administration of GLP-1 Receptor Agonist in Hemodialysis Patients with Type 2 Diabetes Mellitus

MASAO TOYODA, MORITSUGU KIMURA, MASAFUMI FUKAGAWA, *Isehara, Japan*

Dulaglutide was launched in Japan in September 2015. This GLP-1 receptor agonist is administered once a week, and can be used regardless of renal function and in combination with other glucose-lowering agents. Previous pharmacodynamics studies compared single subcutaneous dose of dulaglutide at 1.5 mg/week in subjects with renal dysfunction and those with normal renal function. The results did not show significant difference in any of the pharmacokinetic parameters between the renal dysfunction and normal groups. There is no information so far on the efficacy and safety of dulaglutide in hemodialysis patients with T2DM.

To determine the effects of dulaglutide on various markers of blood glucose variability, safety and quality of life (QoL) in hemodialysis diabetic patients.

The subjects were hemodialysis patients with T2DM treated with dulaglutide since September 2015 at 0.75 mg/week. These patients were switched from insulin therapy or liraglutide therapy. Blood glucose variability was assessed using various laboratory tests, self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM).

In all patients, treatment with dulaglutide either did not change or improved various parameters of blood glucose variability, such as M-values and SD, as measured by SMBG and CGM, compared to those measured under previous treatment. No side effects, such as hypoglycemia, were observed during the treatment period.

We conclude that dulaglutide is effective in the treatment of T2DM during hemodialysis, and improved QoL, based on reduction in the number of injections. Our findings suggest that dulaglutide is a potential glucose-lowering option for glycemic control in dialysis patients.

1065-P

Pharmacokinetic and Pharmacodynamic Profiles of YH25348, a Novel Long-Acting Fc-FGF-21 Analogue

JUN H. KIM, HYUN H. CHOI, DOHOON KIM, SEYOUNG LIM, MINJI SEO, MI K. JU, JU-YOUNG PARK, BYUNG H. CHOI, JONG G. KIM, SU Y. NAM, *Seoul, Republic of Korea*

Fibroblast growth factor-21 (FGF-21) is a promising candidate for the treatment of metabolic diseases. However, due to its short half-life in circulation, frequent doses are required to maintain steady-state plasma concentrations within an appropriate therapeutic range. Also, FGF-21 was found prone to form self-aggregation. YH25348 is a novel Fc-fused FGF-21 analogue, engineered for increased *in vivo* half life and resistance to self-aggregation. Pharmacokinetic parameters were evaluated in mice and monkeys following subcutaneous (SC) administration of YH25348. The serum half-life was found to be significantly extended when compared to wild-type FGF-21. After single SC injection of YH25348, a sustained and dose dependent glucose lowering effect was observed in ob/ob mice. In db/db mice and low-dose streptozotocin-treated mice fed with high-fat diet, YH25348 also elicited potent and sustained glucose lowering and weight loss following single SC injection. In diet-induced obese mice, YH25348 caused significant body weight loss following 2-week repeat dosing (Q4D x 3 times). Furthermore, *ex vivo* T cell activation assays indicate that YH25348 has a low potential risk for clinical immunogenicity. These findings provide a compelling rationale for the further development of YH25348 as a novel therapeutic for the treatment of metabolic diseases.

1066-P

WITHDRAWN

1067-P

The Effect of Glucagon-like Peptide-1 (GLP-1) Receptor Agonists (GLP-1RA) on Postprandial Glucagon Secretion Independent of the Gastric Emptying Rate

CHRISTIAN S. FRANDSEN, LAUGE ØSTERGAARD, THOMAS F. DEJGAARD, BO SØNDERGAARD, JENS J. HOLST, STEN MADSBAD, *Hvidovre, Denmark, Gentofte, Denmark, Copenhagen, Denmark*

GLP-1 delays gastric emptying (GE) and inhibits glucagon secretion. The emptying effect rapidly shows tachyphylaxis during liraglutide treatment whereas it is sustained with exenatide. The effect of GLP-1 on glucagon secretion independent of the GE rate is largely unknown. We investigated the glucagonostatic effect of the short- and long-acting GLP-1RAs, exenatide and liraglutide, respectively, independent of the GE rate in order to see whether the glucagonostatic effect would also show tachyphylaxis with liraglutide and remain intact during exenatide treatment.

We conducted a randomized study, in which 8 persons with type 1 diabetes (T1D) (mean±SD; age 39±6 years, BMI 24.5±3.5 kg/m^2, HbA1c 68±11 mmol/mol, diabetes duration 19±10 years, and C-peptide negative) were given a liquid meal (Boost, Nestlé, 240 Kcal) administered by gastroscopy directly into duodenum over 3 minutes at baseline and after two weeks´ crossover treatment with liraglutide 1.2 mg once daily/exenatide 10 µg twice daily as add-on to insulin treatment. The primary outcome was postprandial glucagon responses (measured using a C-terminal glucagon assay).

Postprandial glucagon total areas-under-the-curve (AUCs) did not differ between baseline (1735 pM x 240 min), or during liraglutide (1552 pM x 240 min; p=0.45 vs. baseline) or exenatide treatment (1663 pM per 240 min; p=0.62 vs. baseline), respectively. Postprandial glucose incremental AUCs were similar on the experimental days; 1112 mM x 240 min at baseline, 1082 mM x 240 min with liraglutide (p=0.18 vs. baseline) and 1235 mM x 240 min with exenatide (p=0.64 vs. baseline).

In conclusion, neither liraglutide nor exenatide suppressed postprandial glucagon secretion or altered plasma glucose excursions when differences in GE rates were prevented, suggesting that neither short nor long-acting GLP-1RA´s act directly upon duodenally stimulated glucagon secretion in C-peptide negative patients with T1D.

1068-P

Underlying Superagonistic Mechanisms of Efpeglenatide in Glyceamic and Weight Loss Potencies

IN YOUNG CHOI, SUNG HEE PARK, MI JIN MOON, JIN YOUNG KIM, YOUNG MI LEE, MICHAEL TRAUTMANN, SE CHANG KWON, *Hwaseong, Republic of Korea, Chula Vista, CA*

Efpeglenatide is a long-acting GLP-1 receptor (GLP-1R) agonist developed for the treatment of type 2 diabetes. It consists of an exendin-4 analog and human Fc fragment conjugated via non-peptidyl linker. As previously reported, efpeglenatide possesses a superagonistic property that activates the GLP-1R without triggering immediate receptor internalization and subsequent degradation. In this study, we investigated additional evidence of superagonism and beneficial effects on pancreatic β-cells through *in vitro* and *in vivo* studies. The attenuation of GLP-1 signaling is due to internalization of GLP-1R, therefore the β-arrestin-2 recruitment and receptor internalization by efpeglenatide were assessed in GLP-1R overexpressing cells. In addition to 3 to 5 fold less β-arrestin-2 recruitment, significantly more GLP-1Rs remained on the cell surface (68%) after 1 hr treatment of 100 nM efpeglenatide when compared with dulaglutide and liraglutide (31% and 26%). Subsequently, efpeglenatide lead to greater maximum cAMP accumulation overtime, while cAMP accumulation following dulaglutide and liraglutide reached its max after 90 min. We also assessed the β-cell protective effects of efpeglenatide. Efpeglenatide restored insulin secretion and improved the cell survival in INS-1E cells in the presence of high glucose or thapsigargin. After 12 weeks of treatment, efpeglenatide protected from β-cell degeneration and showed glycemic improvement in 12 weeks old *db/db* mice. The above benefits were translated into more potent glucose lowering with greater weight loss in *db/db* mice and DIO mice. Efpeglenatide demonstrated superior HbA1c reduction (-3.8% vs. liraglutide -2.6% and dulaglutide -2.8%) as well as superior weight loss (efpeglenatide -20.9% vs. liraglutide -18.6% and dulaglutide -7.1%) after 4 weeks of treatment. These results suggest that the superagonism of efpeglenatide enhances GLP-1 receptor signaling and consequently leads to superior efficacy.

For author disclosure information, see page A696.

1069-P

Albiglutide, a Weekly GLP-1 Agonist, Improved Glycemic Parameters in Japanese Type 2 Diabetes Mellitus (T2DM) Patients over 1 Year When Added to Single Oral Antihyperglycemic Medications

INAHA OKUDA, TIMOTHY H. WILSON, LIN YUE, HIRO NAKAJIMA, MOLLY C. CARR, MAHO TSUBOI, ANTONIO NINO, *Tokyo, Japan, Research Triangle Park, NC, Collegeville, PA*

Albiglutide (ALBI), a GLP-1 mimetic, is approved to treat T2DM. This Phase 3, 1-year study assessed the safety and efficacy of ALBI in combination with an oral antidiabetic drug (OAD: sulfonylurea [SU; n=120], biguanide [BG; n=67], glinide [GLN; n=65], thiazolidinedione [TZD; n=61], or α-glucosidase inhibitor [aGI; n=61)]. Patients failing monotherapy on OADs were enrolled. The dose of background OAD was not changed during the study except for SU and GLN, which could be downtitrated if hypoglycemia occurred. ALBI was started at 30 mg and uptitrated to 50 mg after week 4 in 53.2% of patients, according to HbA_{1c} or fasting plasma glucose (FPG) criteria. Mean baseline HbA_{1c} was 8.08% (ranging from 7.83% in the BG group to 8.18% in the aGI group). The greatest change from baseline (CFB) in HbA_{1c} at 52 weeks after the addition of ALBI was seen with TZD (–1.42%) followed by aGI (–1.39%); SU (–1.04%); GLN (–0.95%); and BG (–0.94%). HbA_{1c} <7% was achieved in >50% of patients in all groups. Mean reductions in FPG were also observed in all groups. CFB in body weight ranged from 0.52 kg with ALBI+TZD to –0.33 kg with ALBI+BG. Safety was the primary objective: 78.6% (294/374) of patients reported adverse events (AEs) and 2.1% (8/374) had a serious AE (SAE) during the study. The incidences of AEs and SAEs were similar across all groups. Common AEs were nasopharyngitis (32.6%), constipation (7.2%), and diabetic retinopathy (5.3%). No SAEs occurred more than once or were reported in >1 patient. Hypoglycemia was reported in 6.4% (24/374) of patients; most occurred in the ALBI+SU group (17/120; 14.2%) followed by the ALBI+GLN group (4/65; 6.2%). In conclusion, when used in combination with an oral antihyperglycemic medication in Japanese patients, ALBI improved glycemic parameters with less body weight increase. No new safety concerns were detected (NCT01777282).

Supported By: GlaxoSmithKline

1070-P

Changes in Glucose Control Associated with Progression of T2D Over 3 Years: Exenatide Once Weekly vs. Basal Insulin

MICHAEL E. TRAUTMANN, ELISE HARDY, JITEN P. VORA, TIM LIN, RICHARD W. SIMPSON, *Hamburg, Germany, Gaithersburg, MD, Liverpool, United Kingdom, San Diego, CA, Box Hill, Australia*

The progressive nature of T2D often requires add-on therapy following initial glycemic control. We investigated glycemic characteristics associated with T2D progression on two injected treatments. Completer data from DURATION-3, a 3 y RCT of T2D patients on Metformin ± sulfonylurea and exenatide once weekly (QW; 2 mg) or insulin glargine (titrated to a fasting glucose [FG] of 72-99 mg/dL) were analyzed post hoc. We defined responders as patients achieving A1c <7% and progressors as responders with a subsequent A1c ≥7%. At week 26, more patients reached A1c <7% with exenatide QW (140/170 completers) than with glargine (105/163 completers). The number of progressors in both treatment arms increased over time. At 3 y, the ratio of nonprogressors to progressors was higher for exenatide QW than glargine (Table; $p<0.05$). Mean FG at 3 y was higher for progressors than nonprogressors ($p<0.05$) and for progressors on exenatide QW vs. glargine ($p<0.001$); exenatide QW dose was constant but glargine dose increased for progressors (+31 IU) and nonprogressors (+28 IU). PPG was similar at 3 y for progressors on both drugs; for nonprogressors, 2-h PPG was lower with exenatide QW than glargine ($p<0.001$). Overall, more patients were stable on exenatide QW than glargine. The higher FG when progressing on exenatide QW may indicate progressive failure of β-cell responsiveness and guide selection of future therapy.

Table. Baseline Characteristics and Glycemic Response to Exenatide QW and Glargine.

Parameter	Exenatide QW		Glargine	
	Nonprogressor	Progressor	Nonprogressor	Progressor
Completed 26 weeks:				
n	121	19	91	14
A1c, % (Baseline/26 weeks)	8.0†/6.4*	8.0/7.3†	7.8/6.4*	8.1/7.0
FG, mg/dL (Baseline/26 weeks)	163.5/122.2*	179.5/174.7†	165.2/116.7*	159.1/133.5
2-h PPG, mg/dL (Baseline/26 weeks)	201.5/142.6†	189.4/164.5	203.9/153.4	198.0/155.2
Completed 3 years:				
n‡	56	73	35	87
A1c, % (Baseline/3 years)	7.9/6.4*	8.2/7.5	7.6/6.5*	8.2/7.5
FG, mg/dL (Baseline/3 years)	159.9/118.2*	174.4/157.6†	162.1/111.8*	174.1/132.6
2-h PPG, mg/dL (Baseline/3 years)	198.3/130.9†	203.0/185.0	199.9/156.5	208.1/188.8

FG, fasting glucose; PPG, post-prandial glucose; QW, once weekly. *$p<0.05$ vs. progressors within treatment group; †$p<0.05$ vs. glargine within progressor/nonprogressor group; ‡$p<0.05$ comparing the ratio of progressors to nonprogressors for exenatide QW vs. glargine.

Supported By: AstraZeneca

1071-P

Pharmacokinetics and Pharmacodynamics of Once-Weekly Dulaglutide in a Chinese Population

CORINA LOGHIN, LAI SAN THAM, ARCHANA CHAUDHARY, XUEWEI CUI, JIA LI, *Indianapolis, IN, Singapore, Singapore, Shanghai, China*

This was a 2 part, double-blind study in native Chinese subjects randomized to receive subcutaneous injections of placebo or dulaglutide (0.5, 0.75 or 1.5 mg). Part A was a single dose (SD), 3-treatment period crossover design in healthy subjects (HS, N=16) and Part B was a 4-week, once-weekly multiple-dose (MD), parallel design in patients with type 2 diabetes (T2D, N=42). Pharmacokinetic (PK) (both parts) and pharmacodynamic (PD) (Part B) evaluations were conducted. PD analyses included glucose, insulin and glycated hemoglobin (A1c).

Following SD administration of 0.5, 0.75, or 1.5 mg dulaglutide to HS, the geometric mean maximum concentrations (C_{max}) were 29.4, 44.2, and 81.5 ng/mL, respectively, with a median time to C_{max} (t_{max}) of ~48 hours (all doses). Following MD in T2D patients, dulaglutide mean C_{max} values were 26.3, 41.4, and 70.2 ng/mL, with accumulation ratios of 1.33-1.39. SD and MD exposures were generally dose-proportional across the 0.5-1.5 mg range. A geometric mean for half-life of 4-5 days was seen across all MD groups.

In Part B, following MD administration, statistically significant reductions in baseline-corrected fasting glucose (-1.17 and -1.41 mmol/L; p=0.003 and p<0.001, respectively) were observed in dulaglutide 0.75 and 1.5 mg compared to placebo on Day 24 and were maintained for 7 days postdose. Statistically significant reductions in baseline-corrected A1c (-0.57 to -0.78%; p<0.001 to 0.008) compared to placebo were observed on Day 29 (1.5 mg) and Day 43 (0.75 and 1.5 mg).

Dulaglutide doses were well tolerated in Chinese subjects. Most adverse events were gastrointestinal disorders and mild in severity. Based on the PK and PD results, dulaglutide can be administered once weekly to Chinese patients with T2D.

1072-P

Update on BCG Clinical Program for Reversal of Established Type 1 Diabetes

DENISE L. FAUSTMAN, *Charlestown, MA*

The bacillus Calmette-Guerin (BCG) vaccine represents the most continuously used and safest vaccine in world history, first used over 100 years ago for tuberculosis prevention. Currently, 10 human clinical trials globally are testing repeat BCG vaccination in diverse forms of autoimmunity and allergies for both prevention and treatment (including patients with new onset and long standing conditions). Phase I study of the BCG vaccine in longstanding type 1 diabetics (T1D) reveals potential disease modulating effects after repeated BCG vaccination, including death of autoreactive cells, transient and modest restoration of insulin secretion and induction of beneficial regulatory T cells (Tregs). A Phase II clinical trial using multi-dose BCG in longstanding T1D was initiated in June 2015. This double-blinded, placebo controlled immuno-interventional trial protocol was approved by the FDA and is unique in testing the efficacy of the BCG vaccine in long-term diabetic subjects (average disease duration: 15-20 years) with small but detectable levels of C-peptide secretion from the

pancreas. Based on published Phase II clinical trial data of BCG in multiple sclerosis subjects, the therapeutic effects of this vaccine appear to improve over the passage of time; therefore, potential clinical benefits in the diabetes trial will be followed for 5 years. The primary endpoint is decrease in HbA1c in treated vs. placebo subjects. The selection of BCG as an immuno-intervention in T1D is based on the protective host TNF response, including induction of Tregs, and potential long-term modulation of the immuno-inflammatory profile of vaccinated subjects.

1073-P

Duodenal-Jejunal Bypass Protects against Streptozotocin-induced Pancreatic Function Failure in Rats

TINGFENG WANG, BO YU, XIONG ZHANG, DAN YANG, ZHENGDONG QIAO, YUEQIAN WANG, TING CAO, LILI GAO, YONGJUN LIANG, LIHUA CHEN, CHENGZHU ZHENG, PENG ZHANG, *Shanghai, China*

Preservation of beta-cell function and promotion of pancreatic beta-cell regeneration have been increasingly appealing in the treatment of both type 1 and type 2 diabetes mellitus. It is still elusive how bariatric surgery affects pancreatic beta cell apoptosis and regeneration. We hypothesize that the internal environment changes induced by intestinal re-routing, including hormonal and cytokine changes, lead to protective and promotional effects on pancreatic beta cells. Forty-six normal SD rats were randomly assigned into three groups: duodenal-jejunal Bypass (DJB) group (n=16), sham group (n= 18), and control group (n=12). Ten days later, streptozotocin (STZ, 45 mg/kg body weight) was injected intraperitoneally into each animal to selectively induce pancreatic beta cell necrosis. Body weight, food intake, plasma glucose level and oral glucose tolerance test (OGTT) were measured. In addition, plasma insulin and GLP-1 levels were also assayed. At the end, pancreas were sliced and stained for beta cell analysis. Animal body weight in three groups did not show significant difference among all three groups at any time points measured, despite that sham and control animals consumed more food than DJB animals on 10th and 28th day after STZ injection. Animals undergoing DJB procedures did not experience typical symptoms of uncompensated diabetes including hyperphagia and progressive weight loss. After STZ injection, not only fasting plasma glucose level remained normal in DJB animals, which was significantly lower than sham and control animals, when challenged by glucose load, did DJB animals also show better glycemic excursion and incretin response when compared to sham and control animals. In addition, pancreatic beta cell mass was obviously better preserved in DJB animals. By re-routing intestine, DJB procedure is capable of protecting pancreatic beta cell from necrosis, and as a result, the animals has better glycemic control and onset of diabetes is delayed.

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1074-P

Glucagon-like Peptide-1 Receptor Agonists Improve Liver Dysfunction in Type 2 Diabetes, Independent of Glycemic Control and Body Weight Loss

YASUKI NAGAI, SHIGERO HOSOE, KANA INOUE, TSUNEHIKO YAMAMOTO, *Amagasaki, Japan*

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) therapies have demonstrated efficacy and safety in the treatment of type 2 diabetes (T2D). Recent studies suggested the potential roles of GLP-1 RAs in the management of nonalcoholic fatty liver disease (NAFLD), but their efficacy and mechanism are not enough elucidated. We investigated the effects of GLP-1 RAs on liver function in T2D patients. This open-label, single-arm trial was conducted in our single medical hospital. Patients with specific liver diseases, including viral, autoimmune and alcoholic hepatitis were excluded. A total of 45 patients (mean age 52.3±12.3 years, hemoglobin A1c [HbA1c] 9.48±1.85%, BMI 32.3±6.5 kg/m^2, diabetes duration 5.5±5.0 years) received GLP-1 RAs, liraglutide (0.9 mg daily) or exenatide (20 μg daily). Any change in the medication of oral hypoglycemic agents was not prohibited during the period of this trial. After 6 months of treatment, changes in HbA1c, body weight, platelet count, liver function and FIB4 index (as a marker of advanced fibrosis based on age, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] and platelet count) were evaluated. Mean HbA1c decreased from 9.48 to 7.31% (P<0.01), body weight decreased from 86.6 to 83.5 kg (P<0.01), significantly. Platelet count increased from 20.6 to 21.5×10^4/μL (P<0.05). AST and ALT decreased from 36.5 to 26.7 IU/L and 51.5 to 33.4 IU/L (respectively, P<0.01). FIB4 index decreased from 1.49 to 1.32 (P<0.05). However, there was significant positive correlation neither between the reduction of ALT and HbA1c (R^2=0.03, p=0.23), nor between the reduction of ALT and body weight (R^2=0.01, p=0.58). These results suggest that GLP-1 RAs improve liver dysfunction in T2D, independent of glycemic control and body weight loss.

1075-P

Treatment Effectiveness up to 24 Months following Initiation of Exenatide Twice Daily vs. Basal Insulin among Type 2 Diabetes Patients in UK Primary Care

CHRISTOPHER L. MORGAN, QING QIAO, SUSAN GRANDY, KRISTINA M. JOHNSSON, SARA JENKINS-JONES, CRAIG J. CURRIE, *Cardiff, United Kingdom, Mölndal, Sweden, Gaithersburg, MD*

Glycaemic and weight change outcomes were compared for type 2 diabetes patients treated with either exenatide twice daily (BID) (Byetta) or basal insulin. Retrospective data (2010-14) were extracted from the Clinical Practice Research Datalink; a UK primary care database. Patients previously naïve to injectable therapy initiating exenatide BID or basal insulin were matched by propensity score. Absolute and relative change in HbA1c and weight from baseline and the proportion of patients achieving HbA1c <7.0% combined with weight reduction targets of i) any weight loss or ii) ≥5.0% baseline were compared at 6 months and 12-24 months. 3,573 patients initiated exenatide BID and 13,503 initiated basal insulin. Patient numbers for each matched analysis are shown in Table 1. HbA1c decreased at 6 and 12 -24 months with no significant difference between the cohorts (Table 1). Weight decreased for exenatide BID patients at 6 and 12-24 months but increased in the basal insulin group. The difference in weight change was statistically significant at each time-point (Table 1). A significantly greater proportion of exenatide BID patients met the HbA1c/weight reduction targets at both time-points. In this real-world data analysis, exenatide BID was associated with equivalence in glycaemic control and greater weight reduction compared with basal insulin.

Table 1. Change in HbA1c and Weight from Baseline and Proportion Achieving Combined Glycemic and Weight Loss Targets for Patients Initiating Therapy with Either Exenatide BID or Basal Insulin.

	6 months			12-24 months		
	Exenatide BID	Basal insulin	p	Exenatide BID	Basal insulin	p
HbA1c (%) change from baseline						
n	960	960		411	411	
Female (n, %)	425 (44.3%)	423 (44.1%)		178 (43.3%)	173 (42.1%)	
Baseline age (Mean years, (sd))	58.8 (10.3)	59.0 (12.0)		58.9 (9.7)	58.8 (11.9)	
Baseline HbA1c (Mean , (sd))	9.4 (1.5)	9.5 (1.6)		9.3 (1.5)	9.4 (1.7)	
Mean absolute HbA1c change	-0.99	-1.04	0.671	-1.03	-0.93	0.095
Mean relative HbA1c change	-9.2%	-9.2%	0.934	-9.5%	-8.0%	0.053
Weight (kg) change from baseline						
n	808	808		458	458	
Female (n, %)	357 (44.2%)	361 (44.7%)		194 (42.4%)	189 (41.3%)	
Baseline age (Mean years, (sd))	59.1 (9.9)	59.5 (12.1)		58.8 (9.9)	58.4 (11)	
Baseline weight (Mean, (sd))	103.7 (19.3)	101.3 (18.5)		103.4 (18.2)	101.4 (17.2)	
Mean absolute change	-3.46	0.82	<0.001	-4.65	1.71	<0.001
Mean relative change	-3.1%	0.8%	<0.001	-4.1%	1.8%	<0.001
Patients reaching target						
n	626	626		381	381	
Female (n, (%)	279 (44.6%)	298 (47.6%)		161 (42.3%)	157 (41.2%)	
Age (Mean years, (sd))	59.1 (9.8)	59.3 (11.7)		58.8 (9.5)	58.8 (11.5)	
Baseline HbA1c (%)(Mean, (sd))	9.4 (1.5)	9.4 (1.6)		9.4 (1.6)	9.4 (1.7)	
Baseline weight (kg)(Mean, (sd))	102.7 (18.6)	100.2 (18.1)		103.6 (18.3)	102.1 (16.6)	
HbA1c < 7.0% and any weight loss	95 (15.2%)	39 (6.2%)	<0.001	70 (18.4%)	31 (8.1%)	<0.001
HbA1c < 7.0% and weight loss ≥ 5%	63 (10.0%)	16 (2.6%)	<0.001	62 (16.3%)	20 (5.2%)	<0.001

Supported By: AstraZeneca

1076-P

Glycemic Lowering with Albiglutide: Effective at 1 Week and Efficacy Maintained for 1 Year

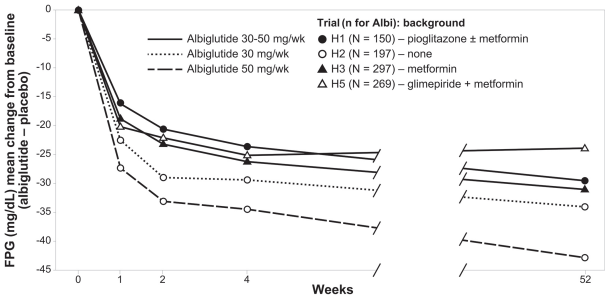
PHILIP D. HOME, ANGELA JONES-LEONE, ANDRE ACUSTA, SERGIO FORERO-SCHWANHAEUSER, *Newcastle, United Kingdom, Philadelphia, PA, Collegeville, PA*

Albiglutide is a long-acting, GLP-1 receptor agonist composed of a dipeptidyl peptidase-4-resistant dimer fused to human albumin. The HARMONY program of eight Phase 3 trials evaluated the efficacy and safety of albiglutide 30-50 mg/week in T2DM. Four trials (HARMONY 1-3 and 5) were double-blind and placebo-controlled, with or without additional active controls (sitagliptin, glimepiride, or pioglitazone). At baseline, participants were ≥18 years old, with HbA1c 7.0-10.0% and creatinine clearance >60 mL/min (Cockcroft-Gault formula). Background therapy varied between studies. Fasting plasma glucose (FPG) change from baseline was a defined secondary endpoint. Across trials, baseline FPG (standard deviation) ranged from 164 (41) mg/dL (H3, placebo arm) to 179 (57) mg/dL (H5, pioglitazone arm). In all four trials, placebo-subtracted FPG levels for albiglutide decreased within 1 week by >15 mg/dL (Figure, *P*<0.0001 vs. baseline for all). At 1 year, placebo-subtracted FPG (95% CI) ranged from –24 (–34, –14) mg/dL for albiglutide 30-50 mg/week in H5 to –43 (–55, –31) mg/dL for albiglutide 50 mg in H2. The proportion of participants experiencing any adverse event was similar between albiglutide and comparators. In conclusion, in people with T2DM, albiglutide lowered FPG from baseline as early as week 1, and levels remained reduced for 1 year.

Supported By: GlaxoSmithKline

For author disclosure information, see page A696.

Figure. Placebo-substracted Mean Change from Baseline in Fasting Plasma Glucose (ITT Population-LOCF) 1-4 and 52 Weeks.*



*P<0.0001 vs baseline for all; Albi, albiglutide; FPG, fasting plasma glucose; H, HARMONY; ITT, intent-to-treat; LOCF, last observation carried forward.

1077-P

Gastric Volume Reduction Is Essential in the Remission of Type 2 Diabetes Mellitus after Bariatric Surgery in Nonobese Rats

XIONG ZHANG, TINGFENG WANG, DAN YANG, ZHENGDONG QIAO, YUEQIAN WANG, TING CAO, LILI GAO, YONGJUN LIANG, PENG ZHANG, *Shanghai, China*

Roux-en-Y gastric bypass (RYGB) has been shown positive outcome in the remission of type 2 diabetes mellitus (T2DM) and weight loss in obese subjects, by inhibiting food intake and nutrients absorption, as well as inducing favorable hormonal changes. The purpose of present study was to investigate whether gastric volume reduction is still required in addition to intestinal bypass for the remission of T2DM in nonobese subjects. Nonobese T2DM Goto-Kakizake (GK) rats were employed in the study. All rats were randomized into three groups according to the surgical procedure performed including 1.) RYGB, 2.) Duodeno-Jejunal Bypass (DJB) without gastric volume reduction, and 3.) Sham surgery. In addition, age-matched Wistar rats were adopted as normal controls. Body weight, food intake, fasting plasma glucose (FPG), and intraperitoneal glucose tolerance test (IPGTT) were measured *in vivo* before and 2, 4, and 8 weeks after the treatment. Whole body metabolic parameters including respiratory exchange ratio (RER), heat production, and activities were also recorded in all animals at 3 weeks postoperatively. Comparing with DJB and Sham animals, RYGB group had lower body weight, less food intake, lower FPG and improved glucose tolerance at all measuring time points postoperatively. By measuring whole body metabolic parameters, we found that RYGB, but not DJB, increased metabolic rate manifested by increased heat production but less activities at night. In the meantime, RER was lower in RYGB group than the other three groups at daytime, meaning adipose tissue became the main source of internal energy production during resting phase in the group. For nonobese T2DM subjects, adding gastric volume reduction to intestine bypass gives better efficacy in remission of T2DM, by increasing metabolic rate and adipolysis, especially during resting period.

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CLINICAL THERAPEUTICS/NEW TECHNOLOGY—ORAL AGENTS

Moderated Poster Discussion: The Oral Agent Pipeline—Which Will Be the Next New Class of Therapies? *(Posters: 1078-P to 1085-P), see page 21.*

1078-P

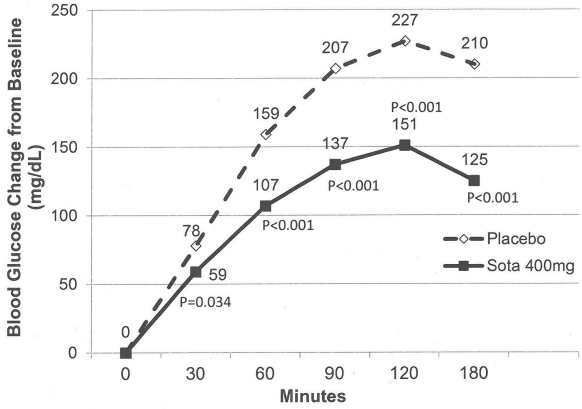
Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, Reduces Late but Not Early Postprandial Glucose Absorption in T1DM: Potential Implications for Recovery from Hypoglycemia

SATISH K. GARG, BRUCE W. BODE, JOHN B. BUSE, WILLIAM T. CEFALU, RUBINA A. HEPTULLA, MARC RENDELL, JULIO ROSENSTOCK, PHILLIP L. BANKS, PABLO LAPUERTA, ARTHUR T. SANDS, BRIAN P. ZAMBROWICZ, PAUL S. STRUMPH, *Aurora, CO, Atlanta, GA, Chapel Hill, NC, Baton Rouge, LA, Bronx, NY, Omaha, NE, Dallas, TX, The Woodlands, TX*

Sotagliflozin (LX4211) is a dual inhibitor of sodium-glucose cotransporters SGLT1 and SGLT2. SGLT1 is the major intestinal glucose transporter. Inhibition of SGLT1 reduces glucose absorption in the gastrointestinal tract whereas SGLT2 inhibition reduces renal glucose reabsorption. Glucose excursions post mixed meal tolerance test (MMTT) were evaluated in 33 T1DM subjects who were randomized to 29 days of double-blind treatment with sotagliflozin 400 mg or placebo, administered 15 minutes prior to the MMTT on day 1 with usual basal insulin but without bolus insulin. Change from baseline blood glucose after the MMTT are summarized in the Figure. Treatment with sotagliflozin provided a highly significant decrease in late-phase postprandial glycemic excursions consistent with SGLT1 inhibition.

In conclusion, these data support that sotagliflozin preserves early-phase absorption of glucose, while decreasing late-phase absorption of glucose. These data suggest that after a meal, sotagliflozin permits the blood glucose increase necessary for recovery from hypoglycemia and may reduce the risk of reactive hyperglycemia associated with treatment of hypoglycemia.

Figure. Blood Glucose Change from Baseline vs. Time after Mixed Meal Tolerance Test.



A standard mixed meal of Boost®, or equivalent was given as 6 mL/kg body weight up to a maximum of 360 mL (for patients >60 kg this is ~60 g carbohydrate, ~15 g protein, and 360 calories.

Supported By: Robert and Janice McNair Educational Foundation

1079-P

GPR40 Agonist MK-8666: A Phase 1b, Randomized, Placebo-Controlled, Multiple-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics in Type 2 Diabetes Mellitus Patients

ALEXANDER W. KRUG, RADHA RAILKAR, BRET MUSSER, JOSEE COTE, TWAN EDERVEEN, ANYA KAUH, PAVAN VADDADY, DANIEL TATOSIAN, PRAJAKTI KOTHARE, *Kenilworth, NJ*

Objective: MK-8666 is a (partial) agonist for the G-protein-coupled receptor (GPR) 40, which mediates free fatty acid-induced insulin secretion in pancreatic beta cells. This study investigated the safety, tolerability, PK and PD of MK-8666 after once-daily multiple dosing in patients with type 2 diabetes.

Methods: 63 T2DM patients were randomized into 4 parallel treatment groups (PBO, n=18; 50 mg, n=9; 150 mg, n=18; 500 mg, n=18). All treatments were administered daily for 14 days. A constrained longitudinal data analysis model was used to analyze the PD data. A semi-mechanistic PKPD model was used to characterize PKPD relationships.

Results: MK-8666 generally showed good tolerability with no dose-limiting side effects, no treatment-related hypoglycemia was observed. One subject in the 150 mg dose group showed mild to moderate elevated liver enzyme levels (ALT 4-5X ULN, AST 2-3 X ULN) at the end of the dosing period. The mean apparent terminal half-life (t½) was 22-32 hrs. MK-8666 significantly reduced FPG and WMG in all dose groups. The mean PBO-corrected reduction from baseline in FPG at Day 15 on MK-8666 was 54.1 mg/dL (500 mg), 36.0 mg/dL (150 mg), and 30.8 mg/dL (50 mg). The geometric mean ratios (MK-8666/Placebo) of the fold changes from baseline in 24-hour WMG after 2 weeks of dosing were 0.77 (500 mg), 0.86 (150 mg), and 0.91 (50 mg). PKPD modeling predicted that at 12 weeks, doses of 500 mg and 150 mg would achieve greater than 95% and ~80% of maximum FPG response, respectively.

Conclusions: Consistent with data from Takeda, our results confirm that activation of GPR40 is an effective target for glucose lowering in patients with T2DM. MK-8666 showed good tolerability and robust glucose lowering efficacy with a PK profile suitable for QD dosing. PKPD modeling predicted that at 12 weeks, a dose of 150 mg or higher was likely to be in a therapeutically effective range.

1080-P

RPC8844 Is a Small Molecule GLP-1R Positive Allosteric Modulator for GLP-1 (7-36), GLP-1 (9-36) and Oxyntomodulin, and Enhances Glucose-Stimulated Insulin Secretion from Human Pancreatic Islets

GREG REINHART, BRYAN CLEMONS, HANS DESALE, LISA DVORAK, ESTHER MARTINBOROUGH, MARCUS BOEHM, ROBERT PEACH, FIONA SCOTT, *San Diego, CA*

Glucagon-like peptide 1 receptor (GLP-1R) is a validated drug target for type 2 diabetes (T2D). To date, only peptide agonist drugs requiring subcutaneous administration have been successfully developed. Our strategy was to develop an orally bioavailable small molecule GLP-1R Positive Allosteric Modulator (PAM) that sensitizes GLP-1R to all naturally occurring and physiologically relevant GLP-1R ligands. This includes the most potent ligands, GLP-1 (7-36) and Oxyntomodulin, but also the inactive DPP-IV-cleaved metabolite, GLP-1 (9-36).

In human GLP-1R expressing CHOK1 cells, RPC8844 potentiates cAMP production by GLP-1 (9-36) by 523-fold, Oxyntomodulin by 25-fold and GLP-1 (7-36) by 2-fold. Similar potentiation is observed in the RIN5F rat insulinoma cell line. In a PAM assay with 60 nM GLP-1 (9-36), the EC_{50} of RPC8844 is 50 nM. Saturation binding studies demonstrate that RPC8844 enhances the K_d of GLP-1 (9-36) by 65-fold, from 79 nM to 1.4 nM, which is equivalent to GLP-1 (7-36). Operational Model of Allostery studies confirm an improvement in the K_d of GLP-1 (9-36) ($\alpha = 25$) but also demonstrate a drastic enhancement of cAMP output ($\beta = 26$) by >600%. The RPC8844 PAM activity is biased towards cAMP signaling, with minimal effect on calcium or pERK signaling, or GLP-1R internalization. Finally, RPC108844 synergizes with GLP-1 (9-36), Oxyntomodulin, and GLP-1 (7-36) to stimulate insulin secretion from human pancreatic islets by 111%, 27% and 51% respectively, in a glucose dependent manner.

In conclusion, RPC844 is an orally bioavailable PAM that converts multiple naturally occurring GLP-1R ligands, including an inactive metabolite, into fully efficacious and potent GLP-1R agonists. The predicted in vivo sequelae are enhanced and sustained GLP-1R signaling improving glucose control.

1081-P

Imeglimin Increases Insulin Secretion in Response to Glucose by a Unique Mechanism of Action Depending on NAD Synthesis

SOPHIE HALLAKOU-BOZEC, SEBASTIEN BOLZE, MICHELINE KERGOAT, MICHAEL RODEN, HAROLD E. LEBOVITZ, *Lyon, France, Chilly Mazarin, France, Düsseldorf, Germany, New York, NY*

Imeglimin is a novel glucose-lowering agent improving insulin secretion and insulin sensitivity by targeting mitochondrial bioenergetics. Imeglimin ability to potentiate glucose stimulated insulin secretion (GSIS) was previously shown *in vitro* in isolated pancreatic islets and *in vivo* in diabetic animal models and in type 2 diabetic patients. Imeglimin mechanism of action (MoA) in potentiating GSIS was explored in isolated diabetic GK rat islets. As NAD is pivotal for mitochondrial functions, we studied Imeglimin effects on NAD content. Imeglimin (100µM) rapidly induced a significant increase in NAD content (+131%, p<0.05). To demonstrate Imeglimin effect dependence on NAD and its metabolites, CD38 enzyme siRNA was used. CD38 enzyme catalyzes NAD conversion into active metabolites involved in Ca^{2+} mobilization from lysosomes and endoplasmic reticulum, leading to insulin secretion. Imeglimin had no effect on GSIS in siRNA CD38 islets showing that NAD metabolites are important components for Imeglimin MoA. To find out how Imeglimin induces an increase in NAD content, an inhibitor of a key enzyme of NAD synthesis pathways, the NMNAT enzyme was used as well as inhibitors of both *de novo* (from Tryptophan) and salvage (from Nicotinamide) pathway enzymes, QPRT and NAMPT respectively. Both NMNAT and NAMPT inhibitors abolished Imeglimin potentiating effect on GSIS, while QPRT inhibitor did not. This showed that the salvage pathway of NAD synthesis has a major role in Imeglimin action on GSIS. Use of specific inhibitors targeting main pathways involved in GSIS showed that PLC, K^+-ATP channel and cAMP were not involved in Imeglimin GSIS potentiating action. The above data show that Imeglimin GSIS potentiating effect in diabetic islets is novel and differentiated from known insulin secretagogue agents. Imeglimin increases NAD synthesis from nicotinamide, a key component of mitochondrial well-functioning, leading to increased Ca2+ mobilization and insulin secretion.

1082-P

Clinical Proof of Concept of Glucokinase Activator HMS5552 Achieved in Chinese T2DM: HbA1c Reduction of 1.22% with 100% Response Rate and Improved β-Cell Function

YANHUA DING, HONG ZHANG, XIAOXUE ZHU, GUILIN CHEN, DALONG ZHU, XIAOYING LI, TIANXIN HU, YONGGUO LI, YU ZHAO, GUIYU ZHAO, SHUANG REN, YI ZHANG, LI CHEN, *Changchun, China, Nanjing, China, Shanghai, China*

Glucokinase (GK) is a glucose-sensing enzyme expressed in pancreas and liver that plays a key role in glucose homeostasis. GK expression and function are impaired in T2DM, which causes reduced glucose and insulin sensitivity linked with progressive deterioration of pancreatic function and increased insulin resistance. HMS5552 is a novel dual-acting allosteric GK activator (GKA) that has shown the ability to enhance glucose sensitivity and improve 24-hour glucose control in T2DM. HMS5552 was further evaluated in a randomized, open-label, two-arm, Phase 1c study for its efficacy, safety, dose regimen and Mechanism of Action. In China, 200 T2DM were evaluated and 24 selected based on clinical algorithms developed at Hua Medicine. The selected subjects received HMS5552 75mg QD or 75mg BID for 28 days and their β-cell function and insulin resistance parameters were evaluated on day 32, after 3 days off the trial drug. HMS5552 showed significant glucose lowering effects with mean HbA1c reductions of 1.22% (P<0.001) and 0.79% (P<0.001) under QD and BID treatments, respectively. FPG were reduced by 14% (P<0.01) or 9% with 2-hour PPG reductions of 34% (P<0.001) or 16% (P<0.05) in QD or BID group compared with baseline, which is correlated very well with a 24-hour glucose lowering profile with mean glucose $AUC_{0\text{-}24h}$ reductions of 21% (P<0.001) or 19% (P<0.01) after QD or BID treatment. In the OGTT study conducted on day 32, $\Delta I_{30}/\Delta G_{30}$ increased significantly in both groups accompanied with reduced HOMA-IR and increased HOMA-β, indicating an improvement in β-cell function and a reverse of insulin resistance after treatment. The response rate with reduction of HbA1c ≥0.6% reached 100% in QD group and 83% in combined group. This study supports that HMS5552 has an excellent hyperglycemic control profile for T2DM with a potential to treat the underlying causes of T2DM in patients selected by clinically validated biomarker driven algorithms.

Supported By: Hua Medicine Ltd.

1083-P

Increase in Blood Pressure Measured Using Ambulatory Blood Pressure Monitoring following Treatment with Glucagon Receptor Antagonist, LY2409021, in Patients with Type 2 Diabetes

CHRISTOF KAZDA, JUAN P. FRIAS, IRENE FOGA, XUEWEI CUI, CRISTINA GUZMAN, PARAG GARHYAN, CORY HEILMANN, JIHUI ANNE YANG, THOMAS A. HARDY, *Neuilly, France, Los Angeles, CA, Toronto, ON, Canada, Indianapolis, IN*

Oral glucagon receptor antagonist (GRA) LY2409021 (LY) lowers glucose in patients (pt) with type 2 diabetes (T2D). Increases in blood pressure have been reported for another oral GRA molecule; however, observations with LY have been inconclusive. This 6-wk, Phase 2, randomized, crossover study evaluated the effects of daily LY 20 mg vs. placebo (PL) on systolic and diastolic blood pressure (SBP and DBP, respectively) and mean arterial pressure (MAP) using 24-hr ambulatory BP monitoring (ABPM) in pt treated with diet/exercise ± Metformin (N=133 LY/PL; N=137 PL/LY). Other measures included changes in fasting serum lipids and glycemic control.

At wk 6, LY increased SBP, with a LSM difference of 2.26 mmHg vs. PL (95% CI: 1.11, 3.40; p<.001); thus, noninferiority to PL was not demonstrated. DBP and MAP also increased, with a LSM difference of 1.37 mmHg (95% CI: 0.66, 2.08; p<.001) and 1.67 mmHg (95% CI: 0.86, 2.47; p<.001) vs. PL, respectively. Small but significant changes in serum lipids were also observed with LY (all p<0.05 vs. PL).

Mean A1c at baseline was 7.3%. At wk 6, LY reduced A1c with a LSM difference of -0.49% vs. PL (95% CI: -0.56, -0.42; p<.001).

Our results indicate a small but statistically significant increases in BP, MAP and serum lipids with LY. These effects may limit the clinical utility of LY2409021 as chronic treatment for T2D.

Table.

Variable	LY2409021 vs. Placebo LSM difference, at Week 6	95% CI
24-hr peripheral pulse rate, bpm	0.02	(-0.88, 0.93)
24-hr pulse pressure, mmHg	0.88*	(0.12, 1.64)
Total cholesterol, mmol/L	0.24**	(0.14, 0.33)
HDL cholesterol, mmol/L	0.02*	(0.00, 0.05)
LDL cholesterol, mmol/L	0.10*	(0.02, 0.18)
Triglycerides, mmol/L	0.24**	(0.12, 0.36)

*2-sided p<.05 vs. placebo; **2-sided p<.001 vs. placebo; Abbreviations: CI=confidence interval; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LSM=least squares mean.

Supported By: Eli Lilly and Company

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1084-P

Assessment of PF-06291874 (PF), a Glucagon Receptor Antagonist Administered as Monotherapy for Four Weeks in Patients with Type 2 Diabetes Mellitus (T2DM)

ARTHUR BERGMAN, BEESAN TAN, VEENA SOMAYAJI, ROBERTO A. CALLE, DAVID J. KAZIERAD, *Groton, CT, Cambridge, MA*

The purpose of this study was to investigate pharmacokinetics, pharmacodynamics (PD), and safety following multiple oral doses of PF in patients with T2DM not receiving other antidiabetic drugs. The study was conducted as a randomized, double blind, placebo-controlled, stratified (for concomitant statin use), parallel group trial. PF was administered orally once daily for 4 weeks.

PF C_{max}, C_{min} and AUC increased proportionally with dose. Median T_{max} occurred 6 hours post dose following the Day 28 dose.

Dose-dependent reductions in mean daily glucose (MDG) and fasting plasma glucose (FPG) were observed following 28 days of PF dosing (Table below). Following an MMTT, dose-dependent increases in glucagon and insulin (modest) were observed. PF was safe and well tolerated at all doses evaluated, including minimal incidence of hypoglycemia. No significant changes in LDL-C were observed at doses up to 75 mg; significant increases from placebo were noted at 150 mg. Small, dose-dependent increases in ALT and AST were observed, but the incidence of values >3x ULN was similar to placebo. In conclusion, PF administration as monotherapy was safe and well tolerated, with robust reductions in plasma glucose following 4 weeks of dosing, supporting further clinical development of PF.

Table.

PF Dose (mg)	N	PD Parameters		Laboratory Safety Parameters	
		CFB MDG (mg/dL) [LSMean(90% CI)]	CFB FPG (mg/dL) [LSMean(90% CI)]	% CFB in LDL-C [LSMean(90% CI)]	Incidence of ALT values >3x ULN
0	34	+10.4 (2.3, 18.4)	7.02 (0.7, 13.4)	2.6 (-2.4, 7.6)	1/34
15	35	-30.0 (-37.7, -22.2)	-20.0 (-26.2, -13.9)	2.3 (-2.6, 7.2)	1/35
35	34	-35.2 (-43.4, -26.9)	-29.2 (-35.6, -22.7)	3.0 (-2.2, 8.1)	0/34
75	35	-58.4 (-66.2, -50.7)	-44.4 (-50.6, -38.3)	2.5 (-2.4, 7.4)	2/35
150	34	-57.8 (-65.8, -49.8)	-50.2 (-56.5, -43.8)	14.9 (9.9, 19.9)	1/34

N= Number of Randomized Patients; CFB= change from baseline; LSMean= least Square mean adjusted for baseline; CI=confidence interval; ULN= Upper Limit of Normal.

1085-P

Inhibition of Glucosyl Ceramide Synthase Does Not Improve Body Weight and Insulin Sensitivity in Obese, Insulin-Resistant Nonhuman Primates

PAUL KIEVIT, ULRICH WERNER, CYNTHIA ARBEENY, HANLAN LIU, BING WANG, MARK BREE, JOHN LEONARD, NORBERT TENNAGELS, PHILIP JUST LARSEN, *Beaverton, OR, Frankfurt, Germany, Framingham, MA, Waltham, MA*

Studies in several type 2 diabetic rodent models suggested that elevated plasma and tissue levels of glucosylceramide (GL1) are associated with insulin resistance (IR) and impaired glucose homeostasis and lowering GL1 by inhibiting glucosylceramide synthase improves insulin sensitivity and glucose metabolism. Therefore the inhibition of GL1 synthesis by specific glucosylceramide synthase inhibitors (GCSi) might be a potential approach to improve overall metabolism in diabetic patients. In order to demonstrate proof of concept in a setting closer to human, we conducted a confirmatory study in non-human primates (NHP) using a highly potent and selective GCSi.

21 adult male, obese, insulin-resistant Rhesus macaques were stratified into three groups of n=7 according to body weight and HOMA-IR. Animals were treated orally with either placebo or GCSi 0.1 mg/kg or 0.5 mg/kg once daily for 6 weeks. Pharmacokinetcs, effect on GCS downstream ceramide GL1, food intake, body weight and composition as well as metabolic status of the animals were evaluated.

Once daily oral treatment with 0.1 and 0.5 mg/kg GCSi resulted in mean trough plasma conc. of 6 and 20 ng/mL, respectively that were sufficient to reduce plasma GL1 by ~50 and 75% at steady state conditions. 6 weeks oral GCSi treatment did not influence food intake, body weight or body composition. Blood glucose and plasma insulin were not changed by treatment and consequently HOMA-IR was not altered. An IVGTT performed before study start and after 5 weeks of treatment did not show treatment-related differences in blood glucose and plasma insulin AUCs. In summary, the inhibition of GCS over 6 weeks resulted in the expected reduction of glucosyl ceramide GL1. However, this did not translate into an improvement of the metabolic phenotype of obese, insulin-resistant NHPs. This data underlines the importance of translational studies in NHP to increase the probability of success for subsequent human studies.

Supported By: Sanofi

Moderated Poster Discussion: Oral Agents—Short-Term Effects to Long-Term Outcomes *(Posters: 1086-P to 1093-P), see page 14.*

1086-P

Empagliflozin and Microvascular Outcomes in EMPA-REG Outcome

CHRISTOPH WANNER, CHRISTOPHER LEE, HANS J. WOERLE, MICHAELA MATTHEUS, SILVIO E. INZUCCHI, BERNARD ZINMAN, *Würzburg, Germany, Ingelheim, Germany, New Haven, CT, Toronto, ON, Canada*

In EMPA-REG Outcome, empagliflozin, given at a dose of 10 mg or 25 mg in addition to standard of care, reduced the risk of cardiovascular (CV) outcomes vs. placebo (PBO) in patients with type 2 diabetes (T2DM) and high CV risk. We investigate the effect of empagliflozin on microvascular outcomes.

A pre-specified composite microvascular outcome was defined as time to first initiation of laser therapy for retinopathy, vitreous hemorrhage, diabetes-related blindness, or new or worsening nephropathy (defined in Table).

7020 patients were included in the intent-to-treat analysis. Median observation time was 3.1 years. Mean HbA1c (%) was 8.08, 8.07 and 8.08 at baseline and 7.93, 7.81 and 8.16 (adjusted) at week 208 for empagliflozin 10 mg, 25 mg and PBO, respectively. The composite microvascular outcome occurred in a significantly lower percentage of patients on empagliflozin (pooled; 14.0%) than PBO (20.5%; hazard ratio [HR] 0.62 [95% CI 0.54, 0.70]; p<0.001). HR (95% CI) with empagliflozin vs. PBO was 0.69 (0.43, 1.12) (p=0.134) for initiation of laser therapy for retinopathy; 0.93 (0.51, 1.71) (p=0.815) for vitreous hemorrhage; 0.61 (0.53, 0.70) (p<0.001) for new or worsening nephropathy.

Empagliflozin used in addition to standard of care reduced the risk of a composite microvascular outcome in patients with T2DM and high CV risk, driven by a reduction in new or worsening nephropathy.

Table.

Outcome	Placebo		Empagliflozin		Hazard ratio (95% CI)	p-value
	n/N (%)	Rate/ 1000 pt-years	n/N (%)	Rate/ 1000 pt-years		
Composite microvascular outcome	424/2068 (20.5)	83.6	577/4132 (14.0)	52.8	0.62 (0.54, 0.70)	<0.001
Initiation of laser therapy for retinopathy	29/2333 (1.2)	4.4	41/4687 (0.9)	3.0	0.69 (0.43, 1.12)	0.134
Vitreous hemorrhage	16/2333 (0.7)	2.4	30/4687 (0.6)	2.2	0.93 (0.51, 1.71)	0.815
Diabetes-related blindness†	2/2333 (0.1)	0.3	4/4687 (0.1)	0.3	–	–
New or worsening nephropathy	388/2061 (18.8)	76.0	525/4124 (12.7)	47.8	0.61 (0.53, 0.70)	<0.001
New onset of macroalbuminuria	330/2033 (16.2)	64.9	459/4091 (11.2)	41.8	0.62 (0.54, 0.72)	<0.001
Doubling of serum creatinine*	60/2323 (2.6)	9.7	70/4645 (1.5)	5.5	0.56 (0.39, 0.79)	<0.001
Initiation of continuous renal replacement therapy	14/2333 (0.6)	2.1	13/4687 (0.3)	1.0	0.45 (0.21, 0.97)	0.041
Death due to renal disease†	0/2333 (0)	0	3/4687 (0.1)	0.2	–	–

Cox regression analysis in patients treated with ≥1 dose of study drug.
*Accompanied by estimated glomerular filtration rate (Modification of Diet in Renal Disease formula) ≤45 ml/min/1.73m^2. †Hazard ratio and 95% CI were not analyzed as the total number of events was <14.

Supported By: Boehringer Ingelheim and Eli Lilly and Company

1087-P

Effects of Sodium Glucose Cotransporter 2 Inhibitors on Bone Microarchitecture and Bone Mineral Density in OLETF Rats

EUN SOOK KIM, JAE-SEUNG YUN, SUN-AH CHA, HYUK-SANG KWON, SOON-JIB YOO, JE HO HAN, SEUNG-HYUN KO, SUNG DAE MOON, *Incheon, Republic of Korea, Seoul, Republic of Korea*

Objectives: Growing evidence suggests that type 2 diabetes (T2DM) is associated with increased fracture risk. Selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, a currently available antidiabetic medication further, raises a concern for bone health. This study investigated the effects of dapagliflozin on bone microarchitecture and bone marrow density in an animal model of T2DM.

Methods: Lean LETO rats and obese OLETF were divided into the four groups (n = 10/group) for 12 weeks: LETO, control OLETF, OLETF treated with 1 mg/kg/d of SGLT2 Inhibitor dapagliflozin, and OLETF treated with 0.6 mg/kg/d of other antidiabetic drug voglibose. Tibiae and femurs were collected for gene expression of bone markers (RT-PCR) and structure (micro-CT) analysis.

Results: Dapagliflozin treatment showed less increase in body mass compared to controls. Bone micro-CT scan of OLETF rats, a model of T2DM showed a significant impairment in trabecular bone microarchitecture (percent bone volume with respect to total volume, trabecular thickness, trabecular separation, trabecular number, and structure model index) in the proximal femur. These impairments were unchanged after dapagliflozin treatment whereas they were significantly ameliorated by voglibose administration. Dapagliflozin treatment group demonstrated lower BMD compared to control OLETF as well as LETO. Urinary N-telopeptide (U-NTX), a marker of bone resorption, was lower in OLETF than in LETO rats. Dapagliflozin did not change U-NTX levels, whereas voglibose increased these levels, RANKL and OPG mRNA was not different between groups, except slightly increased OPG in OLETF treated with voglibose.

Conclusions: Dapagliflozin did not changed impaired microarchitecture of trabecular bones and showed potential adverse effects on BMD in a diabetic bone disease model. Further clinical and mechanistic studies are needed to clarify effects of dapagliflozin on bone health in humans.

Supported By: Korean Diabetes Association

1088-P

Gastrointestinal and Renal Effects of 3 Months of Treatment with GLP-1 Receptor Agonist Exenatide and DPP-4 Inhibitor Linagliptin: The SAFEGUARD Trial

MILOS MRAZ, JANA KLOUCKOVA, PETRA KAVALKOVA, PAVEL TRACHTA, JARMILA KRIZOVA, MIKULAS KOSAK, IVANA KURZOVA, PETR KOCNA, MARTIN HALUZIK, *Prague, Czech Republic*

Several clinical and experimental trials have raised concerns about potential gastrointestinal (GIT) and renal side-effects of incretin-based therapies. To better characterize their GIT and renal safety profile we have performed a randomized controlled trial comparing the effects of the GLP-1 receptor agonist exenatide, the DPP-4 inhibitor linagliptin and the sulphonylurea derivate gliclazid MR on different GIT and renal parameters as part of the SAFEGUARD (Safety Evaluation of Adverse Reactions in Diabetes) project. 39 subjects with type 2 diabetes mellitus (T2DM) treated with Metformin were randomized to 3 months of treatment with exenatide, linagliptin or gliclazid MR. GIT and renal effects were analysed using a combination of serum (liver and pancreatic enzymes, albumin, cystatin C), fecal (fecal elastase) and urine parameters (albumin, renal damage markers NGAL and KIM-1) with functional tests (^{13}C-mixed triglycerides (MTG) breath test) and glomerular and tubular function measures (glomerular filtration rate, tubular resorption, fractional excretion of sodium and urea). After 3 months of treatment, except of improved glucose control, no change in any of the studied serum GIT and renal parameters could be seen in any of the groups. Similarly, parameters of ^{13}C-MTG test and fecal elastase levels were not affected by any of the investigated substances. The same was true for measures of renal function except of increased glomerular filtration rate in both the exenatide (1.4 ± 0.7 vs. 1.8 ± 1.1 ml/s, p=0.03) and linagliptin group (1.7 ± 0.6 vs. 2.3 ± 1.0 ml/s, p=0.025). We conclude that 3 months of treatment with GLP-1 receptor agonist exenatide or DPP-4 inhibitor linagliptin did not induce any significant negative changes in any of the studied GIT and renal parameters while showing some improvement in renal function, supporting thus their safe use in subjects with T2DM.

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1089-P

Cardiovascular Effects of 3 Months of Treatment with GLP-1 Receptor Agonist Exenatide and DPP-4 Inhibitor Linagliptin: The SAFEGUARD Trial

MILOS MRAZ, EVA CHYTILOVA, JANA KLOUCKOVA, PAVEL TRACHTA, JAN SKRHA, JR., JARMILA KRIZOVA, ONDREJ PETRAK, JAN KRUPICKA, VLADIMIR TUKA, JAROSLAV KUDLICKA, ZUZANA KRATKA, GABRIELA DOSTALOVA, JAN MALIK, MARTIN HALUZIK, *Prague, Czech Republic*

Incretin-based therapies have been associated with several cardiovascular side effects raising thus concerns regarding their safe use in subjects with type 2 diabetes mellitus (T2DM). To better characterize their cardiovascular safety profile we have performed a randomized controlled trial comparing the effects of the GLP-1 receptor agonist exenatide, the DPP-4 inhibitor linagliptin and the sulphonylurea derivate gliclazid MR on different cardiovascular parameters as part of the SAFEGUARD (Safety Evaluation of Adverse Reactions in Diabetes) project. 39 subjects with type 2 diabetes mellitus (T2DM) treated with Metformin were randomized to 3 months of treatment with exenatide (E group), linagliptin (L group) or gliclazid MR (G group). Cardiovascular examinations included transthoracic echocardiography, carotid ultrasound, 24-hour blood pressure monitoring, pulse wave velocity (PWV) analysis and LASER Doppler fluxmetry for the assessment of microvascular function. In contrast to improved glucose control no change in 24-hour heart rate, systolic (sBP) or diastolic (dBP) blood pressure could be seen in any of the groups except of a marginally significant reduction in dBP in G group (72.5 ± 5.4 vs. 68.8 ± 6.0 mm Hg, p=0.043). Similarly, no effect on any of the principal parameters of cardiac and vascular morphology and function including left ventricular ejection fraction and intima-media carotid thickness as well as on microvascular reactivity was present in any of the groups. In contrast to linagiptin and gliclazid MR, exenatide slightly increased peripheral PWV (10.2 ± 2.8 vs. 11.0 ± 2.1 cm/s, p=0.046), while having no effect on central PWV. We conclude that 3 months of treatment with GLP-1 receptor agonist exenatide or DPP-4 inhibitor linagliptin did not induce any significant negative change in any of the studied cardiovascular parameters supporting thus their safe use in subjects with T2DM.

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1090-P

Mortality Findings from the EXAMINE Trial

WILLIAM B. WHITE, STUART KUPFER, CHRISTOPHER P. CANNON, CYRUS R. MEHTA, SIMON R. HELLER, CRAIG WILSON, GEORGE L. BAKRIS, WILLIAM C. CUSHMAN, STEVEN E. NISSEN, RICHARD M. BERGENSTAL, PENNY FLECK, FAIEZ ZANNAD, *Farmington, CT, Deerfield, IL, Boston, MA, Sheffield, United Kingdom, Chicago, IL, Memphis, TN, Cleveland, OH, Minneapolis, MN, Nancy, France*

The EXAMINE trial patients had elevated cardiovascular (CV) risk due to type 2 diabetes and a recent (15-90 days) acute coronary syndrome (ACS). We evaluated the risk of CV death in patients randomized to treatment with alogliptin or placebo and following major non-fatal CV events that occurred during the trial. In 5380 patients, overall rates of CV death were 4.1% for alogliptin and 4.9% for placebo (HR = 0.85, 95% CI, 0.66-1.10). Patients were followed until the first post-randomized non-fatal CV event of myocardial infarction (MI), stroke, hospitalized heart failure (HHF), and hospitalization for unstable angina (UA) and then to death or censoring. Time-updated multivariable Cox models were used to estimate the risk of death following each event. There were a total of 736 patients (13.7%) who experienced at least one first non-fatal CV event (5.9% MI, 1.1% stroke, 3.0% HHF, and 3.8% UA). CV death occurred subsequently in 8.2% of those experiencing an MI event, 20.1% of those experiencing a HHF event, 8.8% of those experiencing a stroke, and 3.4% of those experiencing UA, vs. 3.7% (n = 172) of the 4644 patients without a non-fatal CV event. Compared with patients who did not experience a non-fatal event, the adjusted hazard ratio for death was 1.83 (95% CI, 1.29-2.59, p = 0.006) after MI, 3.91 (95% CI, 2.77-5.51, p < 0.0001) after HHF, 1.74 (95% CI, 0.77-3.94, p = 0.186) after stroke, and 0.81 (95% CI, 0.41-1.58, p = 0.527) after admission for UA. Mortality rates following a non-fatal event were comparable on alogliptin and placebo. In EXAMINE, the majority of deaths occurred in patients who did not experience a non-fatal CV event, although the risk of death was markedly higher following a non-fatal event, particularly HHF. These findings illustrate ongoing opportunities to reduce mortality in patients with type 2 diabetes and CV diseases.

Supported By: Takeda Development Center Americas, Inc.

1091-P

Hypoglycemia Is Associated with Increased Risk of Cardiovascular Events: Results from the EXAMINE Trial

WILLIAM B. WHITE, RICHARD M. BERGENSTAL, CHRISTOPHER P. CANNON, STUART KUPFER, CRAIG WILSON, SIMON R. HELLER, *Farmington, CT, Minneapolis, MN, Boston, MA, Deerfield, IL, Sheffield, United Kingdom*

Hypoglycemia is a known complication of some antidiabetic drugs (although not incretin-based therapies). The cardiovascular (CV) outcomes of patients experiencing hypoglycemia have not been well studied. We evaluated the consequence of reported hypoglycemia on the risk for subsequent major adverse CV events (MACE; CV death, nonfatal myocardial infarction or nonfatal stroke). Patients in the EXAMINE trial (N=5380) were at elevated risk for MACE due to baseline type 2 diabetes and acute coronary syndrome within the 15-90 days prior to study entry. EXAMINE patients were randomized to double-blind alogliptin or placebo in addition to standard antidiabetic treatment (adjusted throughout the trial). Most patients were men (68%), white or Asian (73%, 20% respectively) and the mean (SD) age was 61 (9.9)

For author disclosure information, see page A696.

years. Metformin, sulfonylureas and insulin were commonly used at baseline (66%, 47% and 30% of patients, respectively). During the trial, 354 (6.6%) patients were reported to have hypoglycemia (6.7% with alogliptin and 6.5% with placebo); rates of serious hypoglycemia were low (0.7% with alogliptin and 0.6% with placebo). Using a Cox proportional hazards model adjusted for baseline covariates (age, sex, HbA_{1c}, antidiabetic treatment) and study treatment, we found a significant increase in MACE among patients who developed serious hypoglycemia (12/34 [35.3%)] vs. those who did not (609/5346 [11.4%)] (adj. HR: 2.42, 95% CI: 1.27-4.60; p=0.007). An increase in MACE was also found for patients with any hypoglycemia (64/354 [18.1%)] vs. those without (557/5026 [11.1%)] (adj. HR: 1.38, 95% CI: 1.05-1.80; p=0.019). Hypoglycemia, in addition to being an adverse event for patients, may have negative CV prognostic implications. Further research on the impact of treatment induced hypoglycemia on CV events is warranted.

Supported By: Takeda Development Center Americas, Inc.

1092-P

Magnitude of HbA1c Reduction and Attainment of Early Glycemic Control Predict Cardiovascular Outcomes and Mortality: A Population-based Cohort Study of 24,752 People with Type 2 Diabetes Initiating First Metformin Therapy

REIMAR W. THOMSEN, ELISABETH SVENSSON, LISBETH M. BAGGESEN, LARS PEDERSEN, HELENE NØRRELUND, ESBEN S. BUHL, CHRISTIANE L. HAASE, SØREN P. JOHNSEN, *Aarhus, Denmark, Copenhagen, Denmark*

We investigated the association of early glycemic control with subsequent risk of cardiovascular complications or death in a population-based cohort of 24,752 incident patients with type 2 diabetes and first Metformin initiation.in Northern Denmark, 2000-2012. We used medical databases to examine early glycemic control achieved within the first 180 days, grouped by attainment of HbA1c <6.5%, 6.5-6.9%, 7-7.4%, 7.5-7.9%, ≥8%, and assessed the magnitude of HbA1c change from baseline to 180 days (ΔHbA1c (%) groups: -4, -3, -2, -1, 0, +1, + ≥2). Patients were followed until acute myocardial infarction, stroke, death, emigration, or end of follow-up in 2012, using Cox regression analysis for confounder adjustment. The risk of a combined outcome event increased with increasing levels of early HbA1c control, compared to achievement of HbA1c <6.5%; adjusted hazard ratio (HR) =1.18 (95% confidence interval (CI) 1.07-1.30) for 6.5%-6.9%, HR=1.24 (1.09-1.40) for 7.0%-7.4%, HR=1.34 (1-14-1.57) for 7.5%-7.9%, and HR=1.60 (1.38-1.85) for ≥8%. Results were consistent for individual outcome events, and when stratified on age, gender, cardiovascular history, calendar year of follow-up, and baseline HbA1c. The magnitude of early HbA1c reduction predicted outcome; adjusted HR= 0.73 (0.59-0.91) for Δ=-4, HR=0.80 (0.65-0.99) for Δ=-3, HR=0.91 (0.78-1.07) for Δ=-2, HR 1.01 (0.91-1.12) for Δ=-1, compared to a reference group with no HbA1c change (Δ=0), while a substantially increased risk was seen in patients with increasing HbA1c despite Metformin initiation; HR 1.29 (0.99-1.67) for Δ=+1, and HR=2.59 (1.65-4.10) for Δ=+ ≥2. In conclusion, a large initial HbA1c reduction and attainment of early glycemic control levels are associated with lower risk of cardiovascular complications and death among first-time Metformin initiators.

Supported By: Novo Nordisk Inc.

1093-P

Beta-Cell Response but Not HbA1c Reduction to DPP-4i Treatment Is Dependent on Duration of Diabetes

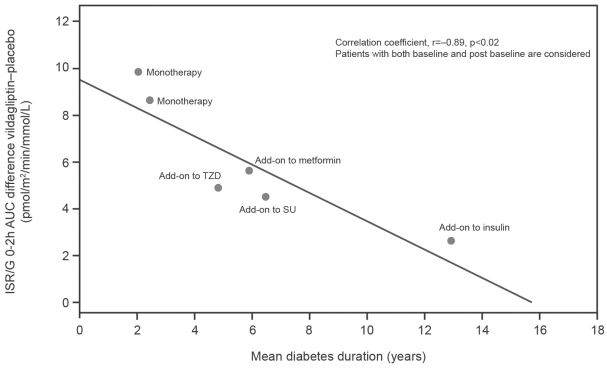
PLAMEN KOZLOVSKI, VAISHALI BHOSEKAR, JAMES E. FOLEY, *Basel, Switzerland, Hyderabad, India, East Hanover, NJ*

DPP-4 inhibitors (DPP-4i) reduce hyperglycemia in type 2 diabetes patients (T2D) by enhancing insulin and suppressing glucagon secretion. Randomized controlled trials, where beta cell response to vildagliptin (V) 50 mg bid was assessed, were analyzed. In each study, the insulin secretory rate (ISR) relative to glucose (G), ISR/G 0-2h, during G load (standard meal or OGTT) was assessed at baseline (BL) and end of study. The mean placebo-subtracted difference (PSD) in the change from BL in ISR/G 0-2h from each study was evaluated as a function of age, duration of T2D (DD), BL ISR/G 0-2h, HbA1c, FPG, BMI, and mean PSD in the change from BL in HbA1c, using univariate model.

There was a strong negative association between the PSD in the change from BL in ISR/G 0-2h and DD (r=–0.89, p<0.02). There was no association between the PSD in the change from BL in ISR/G 0-2h and the PSD in the change from BL in HbA1c (r=0.33, p=0.52). Previously shown lack of association between DD and HbA1c reduction in a larger study pool was replicated in this analysis. None of the other characteristics was significantly associated with ISR/G 0-2h.

These findings indicate that the response of the beta cell but not HbA1c reduction with V is dependent on DD and it can be speculated that glucagon suppression may become the predominant mechanism via which glycemic control is improved when treatment with a DPP-4i such as V is initiated late in the natural course of T2D.

Figure. Association between Adjusted Mean Difference, Vildagliptin 50 mg BID-placebo, in ISR/G Change from Baseline (AUC 0-2h) vs. Mean Baseline Diabetes Duration.



ISR/G, insulin secretory rate relative to glucose; SU, sulfonylurea; TZD, thiazolidinedione

Supported By: Novartis

Moderated Poster Discussion: SGLT2 Inhibitors—Understanding the Benefits and the Risks—And the Beat Goes On *(Posters: 1094-P to 1101-P), see page 15.*

1094-P

Safety and Efficacy of Dapagliflozin (DAPA) in Combination with Potassium (K)-sparing Agents

MIKHAIL KOSIBOROD, JOHN XU, MIKAELA SJÖSTRAND, C. DAVID SJÖSTRÖM, *Kansas City, MO, Gaithersburg, MD, Gothenburg, Sweden*

K-sparing agents are commonly used in patients with heart failure (HF) and hypertension (HTN). SGLT2 inhibitors (SGLT2i) have recently been shown to reduce cardiovascular (CV) mortality and HF events in patients with type 2 diabetes and established CV disease. It is therefore likely that SGLT2i and K-sparing agents will be co-administered - including in patients with HTN and HF. While there are theoretical benefits to co-administration of K-sparing agents and SGLT2i (sodium loss, reduced blood pressure [BP] without increases in heart rate [HR], complimentary effects on neurohormonal axis), it is unclear if such a combination increases hyperkalemia risk. We examined the effects of DAPA 10 mg vs. placebo (PBO) in patients treated with K-sparing agents, using pooled data from 14 phase 2b/3 trials over 24 weeks (DAPA N=108; PBO N=119). Demographics and baseline characteristics were balanced between the groups (mean age 62 yrs, BMI 35 kg/m^2, eGFR ~69 mL/min/1.73m^2, in both groups). DAPA lowered HbA1c, body weight and SBP vs. PBO (Table); the rate of serious adverse events was similar in both groups. No increase in serum K was seen with DAPA; the proportion of patients with K ≥6 mEq/L during follow up was lower with DAPA vs. PBO. When co-administered with K-sparing agents, DAPA resulted in significantly lower HbA1c, weight and SBP, with no evidence of increase in serum K, and lower rate of significant hyperkalemia compared with PBO.

Table. Effects of DAPA on Efficacy and Safety in Patients Receiving Potassium-sparing Agents over 24 Weeks.

	DAPA 10 mg-induced PBO-adjusted ΔBL at Week 24 (95% CI) (N=119 [PBO], 108 [DAPA)]		PBO (N=119)	DAPA 10 mg (N=108)
			n (%)	n (%)
HbA1c (%)	–0.4 (–0.6, –0.2)	AEs of renal impairment/failure*	8 (6.7)	4 (3.7)
Body weight (kg)	–2.2 (–3. 0, –1.4)	AEs of hypotension/dehydration/ hypovolemia*	2 (1.7)	3 (2.8)
SBP (mmHg)	–5.2 (–8.8, –1.6)	Potassium ≥6 mEq/L	9 (7.6)	2 (1.9)
eGFR (mL/min/1.73m^2)	–3.2 (–6.7, 0.4)	Sodium <130 mEq/L	3 (2.5)	0 (0)
Serum sodium (mEq/L)	–0.1 (–0.7, 1.0)	*None were classified as serious AEs. AE, adverse event; BL, baseline; ΔBL, adjusted mean change from baseline; CI, confidence interval; SBP, systolic blood pressure.		
Serum Potassium (mEq/L)	–0.1 (–0.3, 0.0)			

Supported By: AstraZeneca

1095-P

Differential Effects of Dapagliflozin on Cardiovascular Risk Factors at Varying Degrees of Renal Function

HIDDO J.L. HEERSPINK, RAISA KURLYANDSKAYA, JOHN XU, C. DAVID SJÖSTRÖM, *Groningen, Netherlands, Gothenburg, Sweden, Gaithersburg, MD*

SGLT2 inhibition with dapagliflozin (DAPA) decreases HbA1c, body weight, blood pressure (BP), and albuminuria (UACR). Prior studies suggest that the HbA1c lowering effects of DAPA attenuate at lower estimated glomerular filtration rate (eGFR). However, effects on other cardiovascular risk factors at different eGFR levels are incompletely understood. This pooled analysis of 11 phase 3 clinical trials assessed changes in HbA1c, body weight, systolic BP, and UACR with placebo (N=2,178) or DAPA 10 mg (N=2,226) over 24 weeks in patients with type 2 diabetes (T2D), according to baseline eGFR (eGFR ≥45 to <60; eGFR ≥60 to <90; eGFR ≥90 mL/min/1.73m^2). The HbA1c lowering effects of DAPA were smaller at lower baseline eGFR levels (Table). However, the effects of DAPA on body weight and systolic BP were similar regardless of baseline eGFR. Moreover, among individuals with baseline UACR of ≥30 mg/g, the greatest reduction in UACR was observed in patients with an eGFR of ≥45 to <60 mL/min/1.73m^2. Adverse events occurred more frequently in the lowest eGFR subgroup; this was true for both DAPA and placebo treated patients. In conclusion, the HbA1c lowering effects of DAPA decrease as renal function declines. However, DAPA consistently decreases body weight, systolic BP, and UACR regardless of eGFR. These effects suggest that DAPA may confer renal and cardiovascular protection in subjects with T2D and low eGFR.

Table. DAPA 10 mg Induced PBO-corrected Changes on Cardiovascular Risk Factors at Week 24 by Baseline eGFR.

	Difference vs. PBO (95% CI)		
	eGFR ≥45 to <60 mL/min/1.73m^2 (N = 274 [PBO], 252 [DAPA])	eGFR ≥60 to <90 mL/min/1.73m^2 (N = 1233 [PBO], 1251 [DAPA])	eGFR ≥90 mL/min/1.73m^2 (N = 671 [PBO], 723 [DAPA])
HbA1c, %*	–0.27 (–0.43, –0.11)	–0.47 (–0.54, –0.40)	–0.57 (–0.66, –0.47)
Body Weight, kg*	–2.1 (–2.6, –1.5)	–1.8 (–2.0, –1.5)	–2.3 (–2.7, –2.0)
Systolic BP, mmHg*	–4.3 (–6.8, –1.8)	–2.6 (–3.6, –1.6)	–3.4 (–4.7, –2.1)
UACR, %†‡	–38.3 (–54.4, –16.6)	–23.3 (–35.5, –8.7)	–16.1 (–32.3, 3.8)

*Data show mean differences vs. placebo (95% CI) at week 24; †Patients with baseline UACR ≥30 mg/g, data show % differences vs. placebo (95% CI) at week 24; ‡N (PBO/DAPA) = 110/97, 316/322, and 186/179 for eGFR subgroup ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73m^2, respectively. Values exclude data after rescue therapy. BP, blood pressure; CI, confidence interval; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; PBO, placebo; UACR, urine albumin-to-creatinine ratio.

Supported By: AstraZeneca

1096-P

Canagliflozin (CANA) Improves Risk Factors of Metabolic Syndrome (MetS) vs. Sitagliptin (SITA) in Patients with Type 2 Diabetes Mellitus (T2DM) and MetS on Background Metformin (MET) + Sulfonylurea (SU)

MICHAEL J. DAVIES, KATHERINE MERTON, UJJWALA VIJAPURKAR, DAINIUS BALIS, MEHUL DESAI, *Raritan, NJ*

This analysis assessed the effects of CANA, an SGLT2 inhibitor, vs. SITA on the components of MetS in patients with T2DM and MetS. Patients (N = 755; mean age, 57 y; A1c, 8.1%; BMI, 32 kg/m^2) received CANA 300 mg or SITA 100 mg as add-on to MET + SU for 52 weeks. MetS was diagnosed if patients met ≥2 of the following criteria: triglycerides (TG) ≥150 mg/dL; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (men), <50 mg/dL (women); waist circumference (WC) ≥102 cm (non-Asian men), ≥88 cm (non-Asian women), >90 cm (Asian men), >80 cm (Asian women); diagnosis of hypertension or blood pressure (BP)-related criteria (systolic BP [SBP] ≥130 mmHg or diastolic BP [DBP] ≥85 mmHg). At baseline, 78% (n = 586) met the criteria for MetS; proportions were similar across treatment groups. Among patients with data available for all MetS criteria at baseline (n = 584), 37%, 37%, and 18% met 3, 4 or 5 criteria, respectively. CANA 300 mg provided greater reductions in A1c, fasting plasma glucose, SBP, DBP, BW, WC, and BMI vs. SITA 100 mg over 52 weeks (Table). Increases in low-density lipoprotein cholesterol and HDL-C, and reductions in TG were seen with CANA vs. SITA. CANA was generally well tolerated. In summary, CANA improved all components of MetS vs. SITA over 52 weeks in patients with T2DM and MetS on background MET + SU.

Table. Changes from Baseline in MetS Risk Factors at Week 52 (mITT, LOCF).

	CANA 300 mg (n = 289)	SITA 100 mg (n = 297)
Glycemic parameters*		
A1C change, %	–1.1 (0.05)	–0.6 (0.06)
Difference vs SITA	–0.5 (–0.6, –0.3)	
FPG change, mg/dL	–32.6 (2.6)	–4.8 (2.6)
Difference vs SITA	–27.8 (–34.5, –21.0)	
Blood pressure*		
SBP change, mmHg	–5.5 (0.8)	1.1 (0.8)
Difference vs SITA	–6.6 (–8.6, –4.6)	
DBP change, mmHg	–3.2 (0.5)	–0.1 (0.5)
Difference vs SITA	–3.1 (–4.3, –1.9)	
Body composition*		
Body weight change, kg	–2.4 (0.2)	0.3 (0.2)
Difference vs SITA	–2.6 (–3.2, –2.0)	
Waist circumference change, cm	–2.1 (0.3)	–0.02 (0.3)
Difference vs SITA	–2.1 (–2.9, –1.3)	
BMI change, kg/m^2	–0.8 (0.1)	0.1 (0.1)
Difference vs SITA	–0.9 (–1.1, –0.7)	
Lipids*		
LDL-C change, mg/dL	7.2 (1.8)	0.2 (1.8)
Difference vs SITA	7.0 (2.3, 11.7)	
HDL-C change, mg/dL	2.8 (0.4)	–0.01 (0.4)
Difference vs SITA	2.8 (1.7, 3.9)	
Triglycerides change, mg/dL	–3.8 (5.7)	2.1 (5.9)
Difference vs SITA	–5.9 (–21.0, 9.2)	

mITT, modified intent to treat; LOCF, last observation carried forward; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; CI, confidence interval. *Data are LS mean (SE) change from baseline and SITA-subtracted LS mean (95% CI).

Supported By: Janssen Scientific Affairs, LLC

1097-P

Empagliflozin Improves Beta-Cell Function Measured with the Hyperglycemic Clamp in T2DM

HUSSEIN AL JOBORI, GIUSEPPE DANIELE, ROBERT MARTINEZ, MUHAMMAD ABDUL-GHANI, JOHN ADAMS, CURTIS TRIPLITT, EUGENIO CERSOSIMO, RALPH A. DEFRONZO, *San Antonio, TX*

Chronic increase in plasma glucose concentration exerts a deleterious action on beta cell function, i.e., glucotoxicity. The aim of the present study was to examine whether lowering the plasma glucose conc for 2 weeks with empagliflozin (SGLT2 inhibitor) improves beta cell function in T2DM. 15 T2DM patients (age=55±2; BMI= 31.7 ±1.1; FPG=177±8 mg/dl; HbA1c=7.8±0.2%; eGFR=107±7) received empagliflozin (25 mg/day) for 2 weeks, and beta cell function was measured with a 9-step hyperglycemic clamp (each step = +40 mg/dl) before and at 1 and 14 days after the start of empagliflozin. Empagliflozin caused 97±10 and 117±11 grams glucosuria on days 1 and 14, and produced a 45±10 and 40±11 mg/dl reduction (p<0.05 for both) in the fasting plasma glucose concentration, respectively. Empagliflozin caused 29% and 44% increase in the incremental area under the plasma C-Peptide conc curve during the stepped hyperglycemic clamp on days 1 and 14 (from 34±7 to 44±9 and to 49±11 ng/ml.h, respectively, both p<0.01). Empagliflozin also caused an increase in the glucose infusion rate during the hyperglycemic clamp at days 1 and 14 compared to baseline by 2% (P=NS) and 18% (p<0.05), respectively. Beta cell function, measured as the insulin secretion/insulin resistance (IS/IR) index, increased by 29% (p<0.05 vs. baseline) and 69% (p<0.01 vs. baseline) at days 1 and 14 vs. baseline. Empagliflozin also caused a significant increase in beta cell glucose sensitivity during the hyperglycemic clamp (measured as the slope of the line relating the mean plasma C-peptide and plasma glucose conc during each hyperglycemic clamp step) by 37% and 59% at days 1 and 14 compared to baseline.

Conclusion: Lowering the plasma glucose conc with empagliflozin in T2DM patients: (1) enhances tissue glucose uptake during combined hyperinsulinemic/hyperglycemic conditions, (2) augments beta cell glucose sensitivity; (3) improves beta cell function (IS/IR index).

Supported By: Boehringer Ingelheim

1098-P

Impact of Exposure to SGLT2 Inhibitors on Incidence of Diabetic Ketoacidosis among Danish Type 2 Diabetes Patients

MAJKEN L. JENSEN, BENDIX CARSTENSEN, GREGERS S. ANDERSEN, FREDERIK PERSSON, JOHN NOLAN, MARTIN RIDDERSTRÅLE, MARIT E. JØRGENSEN, *Gentofte, Denmark*

The FDA has issued warnings that use of SGLT2 inhibitors may result in diabetic ketoacidosis (DKA), a potentially life threatening acute condition. We investigated the incidence of DKA among patients with type 2 diabetes

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

(T2D) in Denmark, specifically the effect of exposure to SGLT2 inhibitors, other oral antidiabetic drugs (OADs), and insulin. Patients with a diabetes diagnosis identified through national registers (1995 - 2014) in the national patient register, with filled prescription (s) of antidiabetic medication, registered in the Danish National Diabetes Register, or in the Danish Adult Diabetes Database (DADD) were included. Patients with a type 1 diagnosis in DADD or a diabetes diagnosis before the age of 30 were excluded. Drug exposure was taken from the first fill of a prescription. SGLT2 inhibitor exposure only occurred after September 2012. During the 20 year follow-up, 415,670 patients had 4,045 first events of DKA in 3,009,927 person-years, corresponding to a crude incidence rate of 1.34 per 1,000 person-years. The DKA incidence rate decreased by 5.6% (95% CI 5.0%-6.2%) per year. Relative to T2D patients without pharmacological treatment, OAD exposure carried a DKA HR of 1.3 (95% CI 1.2-1.5), insulin exposure a HR of 6.0 (95% CI 5.3-6.8), and the combined exposure of the two a HR of 3.0 (95% CI 2.7-3.4). Exposure to SGLT2 on top of OAD and insulin carried a HR of 2.5 (95% CI 1.1-5.5). The latter is based on 4,524 persons with 6 DKA events during 3,842 person-years of exposure to SGLT2. We conclude that DKA is a real but rare condition in T2D even before SGLT2 treatment was available. The incidence of T2D DKA is decreasing in the Danish population. T2D patients on insulin only have the highest occurrence of DKA, and DKA is more common among those prescribed SGLT2 concomitantly with OADs and insulin, although this association is based on few DKA events and thus far compatible with an excess risk that might not be clinically relevant.

1099-P

Effects of Sodium-Glucose Cotransporter 2 Inhibitor on Carnitine Metabolism in Type 2 Diabetic Patients

MARINA HARADA, MARIKO HIGA, AKEO OHIRA, MOMOKO KANAGUCHI, NAOKO MIYASHITA, AYANO DOI, KAORU YAMASHITA, HIROMI OUCHI, TAKAMASA ICHIJO, *Yokohama, Japan*

Sodium-glucose cotransporter 2 (SGLT2) inhibitors constitute a novel class of antihyperglycemic agents that inhibit glucose reuptake in the kidney, thereby promoting weight loss. A few cases of ketoacidosis resulting from the catabolic processes of metabolism have been reported. Long-chain fatty acids are transported into mitochondria via the carnitine system. More than 95% of carnitine is stored in the skeletal muscles, and acylcarnitine is especially considered an index of beta-oxidation in the skeletal muscles. On the other hand, ketone bodies are said to be the index of beta-oxidation in the liver because they are produced by fatty acid catabolism in the liver. The aim of our study was to understand the metabolic changes in the liver and skeletal muscles by assessing the serum ketone body and carnitine levels after the administration of SGLT2 inhibitor in type 2 diabetic patients. The subjects were 8 patients with type 2 diabetes (age: 44.2 ± 8.2 years, BMI: 32.3 ± 5.7 Kg/m^2). The plasma free fatty acid (FFA), ketone body, and free carnitine and acylcarnitine concentrations were determined 2, 4, and 8 weeks after the administration of ipragliflozin (50mg). Ipragliflozin produced a significant HbA1c reduction (-1.5 ± 1.7%), and body weight reduction (-2.5 ± 2.4 kg) after 8 weeks. The FFA levels significantly increased from 0.6 ± 0.09 to 0.76 ± 0.39 mEq/L, and the 3-hydroxybutyrate levels, from 55.4 ± 40.1 to 189.6 ± 299.6 μmol/L in 4 weeks. The plasma acylcarnitine levels significantly increased from 10.7 ± 3.1 to 14.7 ± 6.6 μmol/L in 4 weeks, which is a peak value. These changes returned to the basal values after 8 weeks. These results suggested that the SGLT2 inhibitor increased fatty acid catabolism in the liver and skeletal muscles in the early stage of an administration of SGLT2 inhibitor. Thus, it is necessary to pay attention to not only ketoacidosis, but also muscle atrophy in patients using SGLT2 inhibitors.

1100-P

Changes in Body Composition and Fatty Liver Markers during SGLT2 Inhibitor Treatment and Their Relevance to the Improvement of Insulin Sensitivity

HITOMI NAKAYAMA, MUNEHISA TSURUTA, SATOMI KAKINO, TAMAMI YOSHIMITSU, SEIKO KAWANO, SHINPEI IWATA, SATOKO YOSHINOBU, MAMIKO KAWAHARA, YUI NAKAMURA, YOSHIE OHTSUKA, YUJI TAJIRI, KENTARO YAMADA, *Kurume, Japan*

In this study we assessed changes in insulin sensitivity together with those in clinical parameters and body composition during the first week of SGLT2 inhibitor treatment. The subjects consisted of 12 male and 9 female inpatients with type 2 diabetes, aged 47±14 years, with a BMI of 29.2±6.6 kg/m^2. Tofogliflozin was administered at the dose of 20 mg/day for 7 days. Insulin resistance was quantified by determining the steady-state plasma glucose (SSPG) concentration during a 180-min infusion of octreotide, glucose, and insulin before the initiation and 2 days after the cessation of the treatment. Body composition was measured by a multi-frequency bioelectrical impedance analyzer (InBody™720). The iPro™ 2 CGM devices were used to monitor subcutaneous glucose levels. Fasting plasma glucose and 24-h average glucose determined by CGM were decreased from 177±43 mg/dL to 120±25 mg/dL and from 186±47 mg/dL to 139±30 mg/dL, respectively (both p<0.0001). SSPG was reduced from 274±81 mg/dL to 228±78 mg/dL (p=0.003). They lost 1.7±1.1 kg of body weight during the treatment (p<0.0001). Body fat mass was reduced by 1.31±0.99 kg (p<0.0001), while no significant change was observed in skeletal muscle mass or body water. However, the muscle mass of the lower extremities was decreased by 0.25±0.39 kg (p=0.007). Among the clinical parameters studied, the reduction of plasma cholinesterase was associated with the reduction of SSPG. Multiple regression analysis showed that the decrease of fasting plasma glucose and the decrease of cholinesterase were independent contributors to the amelioration of insulin resistance (both p=0.03). Thus the decline in body weight during the first week of tofogliflozin treatment was mainly attributable to the decrease of body fat. However, adequate exercise may be required to maintain leg muscle mass. The rapid improvement of insulin resistance was likely caused by the amelioration of hepatic steatosis.

1101-P

Acute Effects of Canagliflozin on Bone Metabolism: Preliminary Results from a Randomized, Placebo-Controlled Trial

JENNY E. BLAU, VIVIANA BAUMAN, PAOLO PIAGGI, MICHAEL T. COLLINS, SIMEON I. TAYLOR, KRISTINA I. ROTHER, *Bethesda, MD*

Sodium-dependent glucose transporter-2 inhibitor (SGLT2i) therapy has been associated with increased treatment-emergent bone fractures. This prompted the FDA to require changes in the label for canagliflozin. The present study evaluates pharmacodynamic mechanisms whereby SGLT2i might affect bone. We employed a randomized crossover design to study healthy adults during two sequential 5-day in-patient stays (NIH Clinical Center) with daily serial blood and urine testing. The primary end-point was the mean of 9 determinations of plasma intact FGF-23 immunoactivity (Immunotopics) between 24-72 hr. We now report results from a pre-planned interim analysis (n=10). As we hypothesized previously, canagliflozin significantly increased serum phosphate within 12hr. Probably triggered by the increase in phosphate, mean FGF-23 (24-72 hrs) increased by 30.8±8.9 pg/mL (+36%; p=0.007, paired t-test). Associated with increases in FGF-23 and/or phosphate, 1, 25-dihydroxyvitamin D levels decreased (Days 2-5; Table 1). Furthermore, PTH increased (Days 4-5), providing evidence of secondary hyperparathyroid physiology. We hypothesize that these endocrine changes could contribute to an increased fracture risk in SGLT2i-treated patients.

Table 1. Placebo-subtracted Changes of Fasting Serum Phospate, 1,25 Vit D and PTH on Days 1-5.

N=10	Day 1	Day 2	Day 3	Day 4	Day 5
Δ Phosphate [mg/dl]	+0.04 ± 0.09	**+0.59*** ± 0.08	**+0.48*** ± 0.11	**+0.16*** ± 0.07	-0.04 ± 0.07
Δ 1,25 Vit D [pg/ml]	+0.29 ± 3.9	**-13.4*** ± 3.5	**-12.4*** ± 4.0	**-17.0*** ± 2.4	**-12.4*** ± 4.0
Δ PTH (intact) [pg/ml]	-0.3 ± 2.6	+0.2 ± 1.9	-0.5 ± 2.5	**+6.4*** ± 2.4	**+6.0*** ± 2.1

Results expressed mean ± SEM; *p<0.05.

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1102-P

Ipragliflozin Improved Cardiometabolic Risk Factors in Japanese Patients with Type 2 Diabetes: A Pooled Analysis of Six Randomized, Placebo-Controlled Trials

ATSUNORI KASHIWAGI, SATOSHI YOSHIDA, ICHIRO NAKAMURA, NORIKO AKIYAMA, KENICHI KAZUTA, EIJI UEYAMA, HIDEYUKI TAKAHASHI, YOSHINORI KOSAKAI, KOSEI KAWAMUKI, *Kusatsu, Japan, Tokyo, Japan*

We examined the impact of cardiometabolic risk factors on outcomes of treatment with ipragliflozin (IPRA), a sodium-glucose cotransporter 2 inhibitor, in Japanese patients with type 2 diabetes. We pooled patient-level data from six Japanese phase II and III trials in which 628 and 368

patients were treated with IPRA or placebo (PBO), respectively (mean age 59.0 and 58.5 years, respectively). Patients were divided into subgroups according to baseline cardiometabolic risk factors (high- and low-risk groups for each). The changes in variables from baseline to end of treatment were compared between IPRA and PBO in each subgroup. Baseline HbA1c was negatively correlated with the change in HbA1c in the IPRA group. HbA1c was unchanged in 11.8% of patients in the IPRA group. The change in HbA1c was weakly correlated with the change in body weight in all patients. HbA1c, fasting serum insulin, HOMA-R, uric acid, and systolic blood pressure decreased, triglyceride tended to decrease, and HOMA-β increased in the low- and high-risk IPRA groups (Table). Liver enzymes improved in the high-risk IPRA groups as compared with the low-risk groups. IPRA was associated with improvements in cardiometabolic risk factors compared with PBO in Japanese patients with type 2 diabetes.

Table. Changes in Clinical Variables from Baseline to the End of Double-blind Treatment with Ipragliflozin or Placebo.

Clinical variables and subgroups	Ipragliflozin			Placebo			Placebo-subtracted difference (*P*-value)
	n	Baseline	Change from baseline	n	Baseline	Change from baseline	
Hemoglobin A1c (%): <8%≥8%	270/356	7.51/8.67	−0.45/−0.92	152/215	7.56/8.72	0.25/0.38	−0.71 (<0.001)/−1.28 (<0.001)
Fasting serum insulin (μU/mL): <6 μU/mL≥6 μU/mL	288/338	3.98/10.76	−0.28/−2.41	185/182	3.76/10.09	0.19/−1.11	−0.40 (0.004)/−0.90 (0.014)
HOMA-R: <2.5≥2.5	301/325	1.61/4.64	−0.28/−1.78	196/171	1.60/4.46	0.20/−0.40	−0.47 (<0.001)/−1.22 (<0.001)
HOMA-β (%): <20%≥20%	244/382	12.5/39.7	4.4/3.1	182/185	12.3/39.3	0.4/−5.2	4.0 (<0.001)/8.7 (<0.001)
Systolic blood pressure (mmHg): <140 mmHg≥140 mmHg	483/143	124.5/148.3	−0.9/−15.0	288/79	123.7/147.3	1.5/−8.7	−2.1 (0.013)/−5.5 (0.003)
Triglyceride (mg/dL): <150≥150 mg/dL	385/243	95.1/246.9	0.3/−49.0	246/122	97.7/242.1	8.9/−14.1	−7.5 (0.022)/−33.7 (0.056)

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1103-P

Assessment of Saxagliptin Efficacy: A Meta-analysis of Phase 2 and 3 Clinical Trials

BOAZ HIRSHBERG, CHERYL WEI, WILLIAM COOK, KRISTINA JOHNSSON, PIA S. POLLACK, CHRISTINA STAHRE, MIKAELA SJÖSTRAND, *Gaithersburg, MD, Mölndal, Sweden, Gothenburg, Sweden*

This meta-analysis of data from 14 phase 2 and 3, 12- and 24-wk, double-blind, placebo- or active-controlled studies (N=4632) evaluated saxagliptin efficacy in patients with type 2 diabetes (T2D) across treatment regimens. Patients received saxawgliptin 5 mg/d or control as monotherapy (n=1196), add-on therapy (n=2139 vs. placebo and n=514 vs. active control), or initial combination therapy (n=619), or saxagliptin 2.5 mg/d or placebo if they had renal impairment (n=164). Mean (SD) baseline A1c for saxagliptin and control was 8.12% (0.91%) and 8.07% (0.88%) for monotherapy vs. placebo, 8.26% (0.95%) and 8.15% (0.93%) for add-on vs. placebo, 8.48% (0.89%) and 8.44% (0.89%) for add-on vs. active control, 9.41% (1.25%) and 9.43% (1.29%) for initial combination therapy, and 8.45% (1.21%) and 8.09% (1.09%) for patients with renal impairment. A1c reduction from baseline was greater with saxagliptin vs. control for all studies combined (mean difference [95% CI]: -0.55% [-0.63%, -0.47%)] and when used as monotherapy vs. placebo (-0.52% [-0.63%, -0.40%)], add-on vs. placebo (-0.55% [-0.69%, -0.40%)], add-on vs. active control (-0.72% [-0.88%, -0.56%)], initial combination therapy (-0.54% [-0.73%, -0.35%)], and in patients with renal impairment (-0.42% [-0.75%, -0.09%)]. Similar reductions in A1c vs. control were noted for patients <65 y (-0.55% [-0.67%, -0.43%)] and ≥65 y (-0.54% [-0.69%, -0.38%)] and for men (-0.54% [-0.69%, -0.40%)] and women (-0.55% [-0.64%, -0.47%)] across treatment regimens. Patients receiving saxagliptin vs. control were more likely to achieve A1c <7% (39% vs. 23%) and A1c ≤6.5% (24% vs. 14%), with similar effects as monotherapy, add-on, or initial combination therapy. Saxagliptin vs. control was associated with reduction from baseline in glucagon AUC and increases in insulin AUC, C-peptide AUC, and β-cell function as assessed by HOMA-2β. Results of this meta-analysis demonstrate consistency of saxagliptin efficacy in different patient subgroups with T2D across treatment regimens.

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1104-P

Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors and Fracture Risk in Patients with Type 2 Diabetes Mellitus: A Systemic Review and Meta-analysis

DARIN RUANPENG, PATOMPONG UNGPRASERT, JUTARAT SANGTIAN, TASMA HARINDHANAVUDHI, *Minneapolis, MN, Rochester, MN*

Sodium glucose co-transporter 2 (SGLT2) inhibitor is the newest developed oral antidiabetic drug for treatment of type 2 diabetes mellitus. It reduces glucose reabsorption in proximal tubule independent of insulin. Because of its potential mechanism that alters calcium and phosphate homeostasis, SGLT2 inhibitor may pose detrimental effect to bone. The effect of SGLT2 inhibitors on fracture risk remains unclear. Our objective aimed to assess fracture risk in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors.

A meta-analysis was performed including all randomized controlled trials with duration of treatment of 24 weeks or longer, enrolling patient with type 2 diabetes mellitus treated with SGLT2 inhibitor comparing to placebo. A literature search was performed using MEDLINE, EMBASE and ClinicalTrial.gov from inception through November 2015. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. Twenty studies enrolling 8,286 SGLT2 inhibitors and 4,178 placebo treated patients, respectively, were included, reporting 87 fractures. The pooled risk ratio of bone fracture in patients receiving SGLT2 inhibitors vs. placebo was 0.67 (95% CI, 0.42-1.07). The statistical heterogeneity was negligible with an I2 of 0%. The pooled risk ratio for canagliflozin was 0.66 (95% CI, 0.37-1.19); dapagliflozin was 0.84 (95% CI, 0.22-3.18) and empagliflozin was 0.57 (95% CI, 0.20-1.59).

The present study did not demonstrate increased fracture risk in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors. Although our finding contrasted to previously reported studies, further careful assessments are needed to clarify whether the skeleton effect of SGLT2 is drug class or patient subgroup specific.

1105-P

Linagliptin Modulates Intra-islet GLP-1 vs. Glucagon Secretion and Production

YANQING ZHANG, GENEVIEVE E. FAVA, MEIFEN WU, WYNN HTUN, VIVIAN A. FONSECA, HONGJU WU, *New Orleans, LA*

Deriving from the same prohormone proglucagon, GLP-1 and glucagon are both produced in pancreatic α-cells. The relative GLP-1 vs. glucagon production in α-cells is dynamic and often altered in diabetic conditions. Linagliptin is a DPP-4 inhibitor that blocks GLP-1 degradation, and thus enhances the incretin effect of circulating GLP-1. The effect of linagliptin on local GLP-1 vs. glucagon production and secretion in pancreatic islets is not clear. In this study, we investigated this matter using primary human islets and animal models. Specifically, we treated human islets isolated from normal, prediabetic and T2D donors with linagliptin, and examined production and secretion of GLP-1, glucagon and insulin. Furthermore, we employed nonobese diabetes mice and streptozotocin-induced diabetic mice to assess whether linagliptin-treatment (3 mg/Kg bodyweight with daily oral administration) affects GLP-1 vs. glucagon production in T1D conditions. We found that linagliptin significantly improved the functionality of β-cells in all human islets. The concentrations of bioactive GLP-1 in the culture media and lysates of linagliptin-treated islets were significantly higher than controls, which is consistent with the inhibitory effect of linagliptin on GLP-1 degradation. Indeed, DPP-4 expression was detected in the isolated islets and pancreatic lysates. Immunofluorescence co-staining of GLP-1 and glucagon showed that linagliptin increased the number of α-cells producing GLP-1 in T2D human islets and mouse T1D pancreas. Glucagon secretion (assessed with culture media and serum) was significantly inhibited in all models, but glucagon production, which was assessed using cell or pancreas lysates, was not significantly changed. Taken together, our study showed that linagliptin treatment upregulated intra-islet GLP-1 production and secretion, suppressed glucagon secretion without affecting its production, and promoted β-cell function in diabetic conditions.

Supported By: Boehringer Ingelheim Pharmaceuticals, Inc.

1106-P

Empagliflozin as Add-on to Linagliptin and Metformin in Patients with Type 2 Diabetes (T2DM): Subgroup Analysis by Region in a 24-Week Randomized Trial

CHRISTOPH WANNER, EBRAHIM NADERALI, MARIO MALDONALDO, ANGELO DEL PARIGI, ROBERT TOORAWA, CHRISTOPHER LEE, *Würzburg, Germany, Liverpool, United Kingdom, Ingelheim, Germany, Ridgefield, CT, Bracknell, United Kingdom*

The efficacy and safety of empagliflozin 10 mg and 25 mg vs. placebo as add-on to linagliptin 5 mg and Metformin in patients with T2DM were assessed in a Phase III study. In an open-label period, patients with HbA1c ≥8.0 and ≤10.5% received linagliptin 5 mg as add-on to stable dose of Metformin (n=606) for 16 weeks. Subsequently, patients with HbA1c ≥7.0 and ≤10.5% were randomized to double-blind, double-dummy treatments with a single-pill combination of empagliflozin 10 mg/linagliptin 5 mg (n=112) or empagliflozin 25 mg/linagliptin 5 mg (n=111), or placebo plus linagliptin 5 mg (n=110) for further 24 weeks. Changes from baseline (randomization) in HbA1c at week 24 were analyzed in subgroups by region.

For author disclosure information, see page A696.

At week 24, empagliflozin 10 and 25 mg were associated with improvements in HbA1c vs. placebo as add-on to linagliptin and a stable dose of Metformin in patients with T2DM in Europe (including Australia and New Zealand), North America, Latin America and Asia (Table). There was no evidence of treatment differences across regions (interaction p value was 0.8830).

Empagliflozin 10 and 25 mg improved glycemic control vs. placebo as add-on to linagliptin and Metformin for 24 weeks in patients with T2DM irrespective of region.

Table.

	Linagliptin 5 mg and Metformin		
HbA1c (%)	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
Europe, n	32	35	34
Baseline (%)	7.66 (0.13)	7.72 (0.11)	7.67 (0.10)
Change from baseline at week 24, %	0.18 (0.16)	-0.78 (0.15)	-0.47 (0.15)
Difference vs. placebo at week 24		-0.97	-0.65
(95% CI)		(-1.39, -0.55)	(-1.07, -0.23)
p-value		<0.0001	0.0025
North America, n	35	37	38
Baseline (%)	8.30 (0.14)	8.30 (0.16)	8.40 (0.14)
Change from baseline at week 24, %	0.46 (0.15)	-0.21 (0.14)	-0.19 (0.14)
Difference vs. placebo at week 24		-0.67	-0.65
(95% CI)		(-1.07, -0.26)	(-1.06, -0.25)
p-value		0.0015	0.0018
Latin America, n	15	14	14
Baseline (%)	8.10 (0.21)	7.91 (0.20)	7.79 (0.16)
Change from baseline at week 24, %	–0.49 (0.24)	–1.14 (0.23)	–1.14 (0.24)
Difference vs. placebo at week 24		–0.65	–0.65
(95% CI)		(–1.31, 0.00)	(–1.32, 0.01)
p-value		0.0502	0.0547
Asia, n	24	23	24
Baseline (%)	7.77 (0.18)	7.87 (0.18)	7.84 (0.18)
Change from baseline at week 24, %	–0.08 (0.17)	–0.85 (0.18)	–0.92 (0.17)
Difference vs. placebo at week 24		–0.77	–0.84
(95% CI)		(–1.25, –0.28)	(–1.32, –0.36)
p-value		0.0022	0.0007

Baseline values are mean (SE). Changes are adjusted mean (SE) based on MMRM (including treatment, baseline estimated glomerular filtration rate, region, visit, treatment by visit interaction, visit by region interaction, treatment by region interaction, and treatment by visit by region interaction as fixed effects, and baseline HbA1c as a linear covariate) in patients who received ≥1 dose of study drug during the double-blind period and had a baseline HbA1c and on-treatment value (observed cases, excluding values after initiation of rescue therapy). Differences vs. placebo are adjusted means. n is the number of patients analyzed, which may include patients who did not contribute a value at week 24, but who had earlier values available. This study was not powered to detect treatment differences between regions.

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1107-P

RPC8844 Is a Small Molecule GLP-1R Positive Allosteric Modulator that Significantly Improves Hyperglycemia and Induces Weight Loss in Type 2 Diabetes Disease Models after Daily Oral Administration

KEVIN DINES, JULIE WILSON, BRYAN CLEMONS, GREG REINHART, JUNKO TAMIYA, SAMANTHA SAWA, HARRY DEDMAN, RACHEL POWELL, BRIAN FERETIC, PHILIP TURNBULL, JENNIFER BROOKS, LIMING HUANG, ENUGURTHI BRAHMACHARY, ADAM YEAGER, GREGG TIMONY, MARCUS BOEHM, ROBERT PEACH, FIONA SCOTT, ESTHER MARTINBOROUGH, *San Diego, CA*

To date, only subcutaneously administered peptide agonists have been successfully developed for the GLP-1 receptor (GLP-1R). Our strategy was to develop an orally bioavailable small molecule Positive Allosteric Modulator (PAM) that sensitizes GLP-1R to all naturally occurring and physiologically relevant ligands, including the inactive but long lived DPP-IV-cleaved metabolite, GLP-1 (9-36). In vitro, RPC8844 potentiates GLP-1 (9-36) by 523-fold, Oxyntomodulin by 25-fold and GLP-1 (7-36) by 2-fold on cAMP production. Consistent with this pharmacology, RPC8844 enhances the amount of insulin secreted from human pancreatic islets, by all three ligands, in a synergistic and glucose dependent manner.

The efficacy of daily oral administration of RPC8844 on glycemic control was assessed after 21 or 28 days in ob/ob mice and weight-stable diet-induced obese (DIO) mice. Compared to vehicle controls, RPC8844 induced a statistically significant reduction in fasting basal glucose (194 vs. 316 mg/dL), oGTT AUEC (64 vs. 91 g/dL/min), HbA1c (Δ-1.56%) and fasting insulin (5 vs. 9 ng/ml) in ob/ob mice. In DIO mice, RPC8844 induced a statistically significant and dose-dependent reduction in fasting basal glucose (165 vs. 244 mg/dL), oGTT AUEC (27 vs. 50 g/dL/min) and fasting insulin (0.6 vs. 2.3 ng/ml). Intriguingly, RPC8844 completely halted weight gain in ob/ob mice, while Sitagliptin had no effect. More strikingly, RPC8844 induced significant weight loss in DIO mice (15 grams; -26% initial body weight), which was superior to daily 0.2 mg/kg s.c. Liraglutide (7 grams; -12% initial body weight). Significant improvements in liver weight and liver enzymes were also observed with RPC8844 in both models. Efficacy was dose-dependent, and maximal at 100 mg/kg/d. In conclusion, we have generated an orally efficacious GLP-1R PAM with in vitro and in vivo pharmacology consistent with direct engagement of GLP-1R.

1108-P

Elderly Latino Patients with Type 2 Diabetes: A Real-World Perspective

ANA L. CAGIDE, DIEGO H. GIUNTA, GIOVANNI BADER, PÄIVI M. PALDÁNIUS, CARLOS O. MENDIVIL, *Buenos Aires, Argentina, Basel, Switzerland, Bogotá, Colombia*

Hispanics/Latinos are the largest minority group in the U.S. while the growing pool of elderly Latinos with type 2 diabetes is seldom enrolled in clinical trials. Data from real-world studies from different regions of Latin America (LatAm) may be used to extrapolate the treatment outcomes in Latino patients now residing in the U.S. or elsewhere. A sub-analysis in ≥65 years old Hispanic patients from 5 different LatAm countries enrolled in EDGE, a non-interventional real-world study, explored the effectiveness and tolerability of a DPP-4 inhibitor (DPP-4i; vildagliptin) vs. comparator OADs after monotherapy failure. The primary composite endpoint was the attainment of HbA1c <7.5% in elderly population without hypoglycemia or weight gain (≥3.0%) at 12 months. Mean age (±SD) in our cohort (n=986) was 71.5±5.6 years, with 57.5% diagnosed prior to age of 65 years, and women predominating over men (1.43:1). Mean BMI was 28.5±4.8 kg/m^2 and baseline HbA1c at which the physician added a second drug was 8.4±1.7%; in 71% as add-on to Metformin. In 16%, Metformin was dosed with eGFR (MDRD) <60 ml/min. Hypertension and dyslipidemia were prevalent while macro- and microvascular complications were under reported: 10.8% and 6.5%, respectively. 77.8% were assigned to receive a DPP-4i, 56% of them as a single-pill combination. 81% of patients with incident diabetes received DPP-4i. The proportion of patients reaching the primary endpoint was higher in the DPP-4i group vs. comparators (84.4% vs. 77.7%, p=0.065). Patients reached more often other glycemic cut-offs in the DPP-4i group; HbA1c <7.0% (61.0% vs. 54.7%, p=0.179) or <8.0% (91.9% vs. 87.8%, p=0.134). There was a difference in weight (-0.09 kg, p=0.028) in the DPP-4i group vs. comparators. Adverse events were infrequently reported. In real-world setting DPP-4 inhibitors may be an attractive treatment choice for elderly co-morbid Latino patients, independent of disease duration, when targeting recommended HbA1c levels without an increased risk of hypoglycemia or weight gain.

Supported By: Novartis

1109-P

Effect of Empagliflozin on Cardiovascular Death in Subgroups by Age: Results from EMPA-REG Outcome

MARTIN RIDDERSTRÅLE, ELVIRA TOURAL, DAVID FITCHETT, SANJA GILJANOVIC KÎS, HANS J. WOERLE, MICHAELA MATTHEUS, BERNARD ZINMAN, SILVIO E. INZUCCHI, *Gentofte, Denmark, Madrid, Spain, Toronto, ON, Canada, Zagreb, Croatia, Ingelheim, Germany, New Haven, CT*

In the EMPA-REG Outcome trial, empagliflozin (EMPA) given in addition to standard of care significantly reduced 3-point major adverse cardiovascular (CV) events (composite of CV death, non-fatal myocardial infarction, non-fatal stroke), CV death and all-cause mortality vs. placebo (PBO) in patients with type 2 diabetes (T2DM) and high CV risk. Here we investigate the effect of age on the reduction in CV death with EMPA.

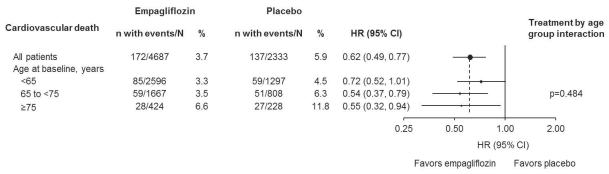
Patients in EMPA-REG Outcome were randomized to receive EMPA 10 mg, EMPA 25 mg or PBO. CV death was analyzed in the pooled EMPA group vs. PBO in subgroups by baseline age (<65, 65 to <75, ≥75 years).

A total of 7020 patients were treated. Median observation time was 3.1 years. Mean (SD) age at baseline was 63.2 (8.8) years in the PBO group and 63.1 (8.6) years in the EMPA group. The benefit of EMPA vs. PBO on CV death was consistent across age categories (Figure). Across age subgroups,

reported adverse events were consistent with the known safety profile of EMPA.

EMPA, in addition to standard of care, reduced the risk of CV death in patients with T2DM and high CV risk irrespective of age.

Figure.



Cox regression model including sex, baseline body mass index, baseline HbA1c, baseline estimated glomerular filtration rate, region, treatment, age group and treatment by age group interaction, in patients treated with ≥1 dose of study drug.

Supported By: Boehringer Ingelheim and Eli Lilly and Company

Clinical Diabetes/ Therapeutics POSTERS

1110-P

DS-8500a, a Novel Orally Active GPR119 Agonist: Nonclinical Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion

TOMOKO ISHIZUKA, TSUNEO DEGUCHI, CHIE MAKINO, YOKO URASAKI, SHINICHI INOUE, OSAMU ANDO, *Tokyo, Japan*

DS-8500a, an agonist of the G-protein coupled receptor (GPR119) expressed in pancreatic beta-cells and intestinal L-cells, is under development for T2DM. The pharmacokinetic properties of DS-8500a were investigated in animals *in vivo* and *in vitro*. After a single oral administration of DS-8500a at 0.3 to 3 mg/kg to Sprague Dawley (SD) rats and cynomolgus monkeys, DS-8500a was rapidly absorbed, with maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increasing more than dose proportionally in both species. The elimination half-life ranged from 2.6 to 3.6 h. The absolute oral bioavailability achieved was over 60%, suggesting good oral absorption. After a single intravenous administration, total body clearance was 3.15 and 7.18 mL/min/kg and the volume of distribution was 0.94 and 1.13 L/kg in SD rats and cynomolgus monkeys, respectively. During an oral glucose tolerance test in Zucker fatty rats, the plasma DS-8500a AUC up to 3.5 h post-dose was 810, 1870 and 4150 ng·h/mL, and C_{max} was 335, 941 and 2000 ng/mL, at effective doses, 1, 3, and 10 mg/kg, respectively. Quantitative whole body autoradiography obtained after a single oral administration of [^{14}C] DS-8500a at 1 mg/kg in SD rats showed whole body radioactivity distribution with the highest level in the liver and low level in the central nervous system. Orally dosed [^{14}C] DS-8500a was equally excreted in urine and feces in SD rats, and the residual in the carcasses was 0.3% of dose at 168 h post-dose. A bile duct-cannulated rat study demonstrated that most of fecal radioactivity was biliary excreted. Plasma protein binding was 98.9% for SD rat, 99.3% for cynomolgus monkey, and 99.8% for human with no concentration dependency. In *in vitro* metabolite analysis, several metabolites were detected in animal and human hepatocyte incubations. No unique human metabolites were detected. In conclusion, these data support to develop DS-8500a as an orally active anti-T2DM agent.

1111-P

Antidiabetic Efficacy of Saroglitazar and Its Combinations with Other Drugs in db/db Mice

MUKUL R. JAIN, SURESH R. GIRI, BIBHUTI B. BHOI, CHITRANG TRIVEDI, AKSHYAYA RATH, PANKAJ R. PATEL, *Ahmedabad, India*

Saroglitazar is a novel dual PPARα/γ agonist that showed significant triglyceride-lowering and insulin-sensitizing effects in various preclinical models. In present study, we have compared the antidiabetic activity of saroglitazar with other antidiabetic drugs in db/db mice, a genetic model of T2DM. Saroglitazar, canagliflozin and sitagliptin were administered to 11-12 week old db/db mice at the dose of 1 mg/kg/day for 8 weeks. Saroglitazar and canagliflozin showed significant 44 and 24% reduction in HbA1c and 63% and 36% reduction in glucose levels, respectively whereas sitagliptin did not showed any significant effect on blood glucose and HbA1c levels. Saroglitazar also showed the significant reduction in serum triglycerides (53%) and non-esterified fatty acids (43%), which was not shown by canagliflozin as well as sitagliptin. The glucose$_{AUC}$ in OGTT study showed that saroglitazar and canagliflozin showed significant 66 and 39% improvements in glucose tolerance whereas sitagliptin showed 27% improvement.

In most T2DM patients, effective management of blood glucose requires combination therapy, hence saroglitazar was evaluated in combination with various antidiabetic drugs like Metformin, dipeptidyl peptidase IV inhibitors (sitagliptin or saxagliptin or vildagliptin), GLP-1 receptor agonist (exenatide or liraglutide) or insulin in db/db mice. Once-daily oral treatment of db/db mice with saroglitazar (0.1 mg/kg) along with other antidiabetic drugs for 14 days resulted in additive or synergistic antidiabetic activity in terms of glucose lowering and improvement in glucose tolerance.

Overall, the results suggest that saroglitazar; an agent approved and available in India for treatment of diabetic dyslipidemia since 2013, showed better antidiabetic activity than canagliflozin and sitagliptin in db/db mice model and also showed additive or synergistic antidiabetic activity with currently available antidiabetic drug having diverse mechanism of action.

Supported By: Cadila Healthcare Limited

1112-P

A Pooled Analysis: Reduction of Hypoglycemic Event Rate with Sitagliptin Compared with Sulfonylurea

JIE LIU, LEI XU, EDWARD A. O'NEILL, SAMUEL S. ENGEL, *Kenilworth, NJ*

Hypoglycemia (HYPO) is a major limiting factor in treating patients (PTs) with T2DM to meet glycemic goals. Sitagliptin (SITA), a DPP-4 inhibitor, has been shown to have a reduced incidence of HYPO compared to sulfonylureas (SU). However, comparison of crude incidences may underestimate the differing burden of HYPO experienced by PTs by discounting multiple events occurring per PT. To further assess this, data were pooled from six randomized, double-blind studies in which PTs with inadequate glycemic control on diet alone ± Metformin were treated with SITA 100 mg/day (or reduced dose in renal insufficient PTs) or an SU (glipizide or glimepiride) and used to compare the glycemic efficacy, and the incidence, event number, event rate, and timing of AEs of symptomatic (Sx) HYPO in each group. All data were from treatment week 30 or the closest data collecting point prior to week 30. A total of 3479 subjects were included in the analysis: 1741 on SITA and 1738 on SU. The baseline characteristics were similar between the groups. At the relevant time point, the reduction from baseline in A1c was -0.53% and -0.64% for the SITA and SU groups, respectively. In the SITA group 49.1% of subjects were at A1c goal of <7% compared with 54.3% subjects in the SU group. The incidence of AEs of Sx HYPO was 20.3% vs. 4.4% with SU vs. SITA, respectively. The event rate was 1.3/patient-year vs. 0.15/patient-year, respectively. The incidence of >1 Sx HYPO event was 12.8% and 1.8%, respectively. In both groups, Sx HYPO incidences and event rates were highest in the first three months of therapy. In this pooled analysis of SITA vs. SU therapy, the incidence of Sx HYPO was 4.6-fold higher and the event rate was 8.7-fold higher with SU relative to SITA. To fully assess the excess patient-burden for HYPO, event-rate, in addition to incidence, should be considered.

Supported By: Merck & Co., Inc.

1113-P

Alpha-adrenergic Blockers Suppress Morning Elevation of Plasma Glucose Levels after Waking

KEISHI YAMAUCHI, YASUTO NAKASONE, TAKAHIRO MIYAKOSHI, YUKA SATO, TORU AIZAWA, *Matsumoto, Japan*

Previously, we reported that morning plasma glucose (PG) elevation before and after wake-up, W1 and W2, respectively, occur through different mechanisms in patients with type 2 diabetes. We measured three point PG; midnight (3 a.m.), the time of awakening (around 6 a.m.) and just before breakfast (around 8 a.m.), serum immunoreactive insulin and insulin-antagonistic hormones, and urinary catecholamines and their metabolites in 32 hospitalized patients with type 2 diabetes. Those with insulin therapy or overtly elevated fasting PG (>11 mmol/L) were excluded. W1 could be explained by relative insulin deficiency. Urinary normetanephrine, reflects a sum of production of norepinephrine was significantly correlated with W2 (R=0.422, p<0.01). Level of other antagonistic hormones including urinary metanephrine was not correlated with W2. Norepinephrine, a relatively selective agonist of alpha-adrenergic receptor, within the normal range, may be responsible for W2. This time 2 mg of doxazosin, an alpha-adrenergic blocker was administered 4 diabetic patients with hypertension at wake-up. As shown in the Figure, amount of change of PG between waking and breakfast in these patients was significantly suppressed. In conclusion, heightened ambient alpha adrenergic tone, within the normal range, may be responsible for the preprandial elevation of PG after waking. Alpha-adrenergic blockers may suppress the elevation.

For author disclosure information, see page A696.

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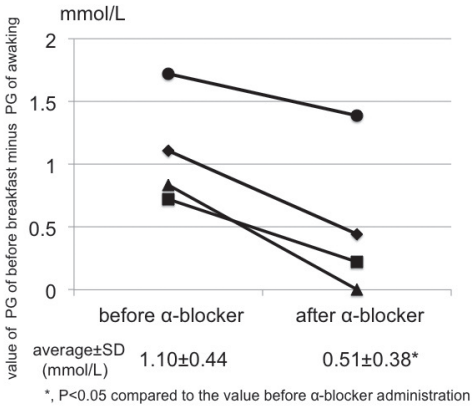
Figure.



1114-P

Current Status of Metformin in Addition to Insulin Therapy in Adult Patients with Type 1 Diabetes Mellitus: An Analysis from the Guangdong T1DM Translational Medicine Study

LILING QIU, JINHUA YAN, DAIZHI YANG, SIHUI LUO, XUEYING ZHENG, WENQIAN REN, SHANSHAN XIONG, LILI JIANG, BIN YAO, JIANPING WENG, *Guangzhou, China*

The previous studies suggested some evidence that Metformin in addition to insulin can lead to the reduction in daily insulin dosage, body weight or improvement of glycemic control in type 1 diabetic patients. We use data from the Guangdong T1DM Translational Medicine Study to describe the current use and efficacy of additional Metformin therapy in patients with type 1 diabetes (T1D).

Type 1 diabetic patients aged ≥ 18 years were included from the Guangdong T1DM Translational Medicine Study, which was a multicenter registry study of T1D in Guangdong, China. Patients with combined insulin plus Metformin therapy (n=90) were compared against those with insulin therapy only (n=897).

Patients with additional Metformin therapy took 1000 mg of Metformin per day on average. At baseline, they were more prevalent with hyperlipidemia (17.8% vs. 8.9%, p = 0.007) and had higher body mass index (BMI) (22.5 ± 3.9 vs. 20.3 ± 2.8 kg/m^2, p < 0.001) than those treated with insulin only. But age, gender distribution, duration of diabetes, HbA1c, daily insulin dosage and waist-hip ratio (WHR) had no statistical difference between two groups. After 1-year's follow-up, HbA1c improved in both groups, but the changes of it were not significantly different between the two groups (-0.7 (-1.7, 0.2) vs. -0.4 (-1.6, 0.4), p = 0.507), while the daily insulin dosage and WHR did not change in both groups. Addition of Metformin resulted in an unchanged BMI, while patients treated with insulin only experienced weight gain with BMI increasing from 20.3 ± 2.8 to 20.8 ± 2.7 kg/m^2 (p < 0.001).

The results suggested that Metformin is initiated more in type 1 diabetic patients with hyperlipidemia or higher BMI in current practice in China. Additional Metformin therapy is effective in keeping weight but does not improve the glycemic control for patients with T1D. Further study is necessary to explore its efficacy and safety in type 1 diabetic patients.

Supported By: Sun Yat-Sen University (2007030); Science and Technology Planning Project of Guangdong Province (2014A020212065); National Health and Family Planning Commission Foundation for Public Welfare (201502011)

1115-P

Chronic Treatment with a Sodium/Glucose Cotransporter 1 and 2 (SGLT1/2) Dual Inhibitor Promotes Body Weight Control in DIO Mice

FUYONG DU, SIMON A. HINKE, NATHANIEL WALLACE, THOMAS KIRCHNER, JEAN WHALEY, GUOZHANG XU, GEE-HONG KUO, MICHAEL D. GAUL, KEITH DEMAREST, YIN LIANG, *Spring House, PA*

Inhibition of sodium/glucose cotransporter 1 and 2 (SGLT1/2) dual improves glycemic control by reducing SGLT1-mediated absorption of intestinal glucose and by increasing SGLT2-mediated renal glucose excretion. To determine if SGLT1/2 dual inhibition promotes body weight control, we tested the effect of chronic treatment of CmpdA, a SGLT1/2 dual inhibitor, on the body weight gain of mice fed high fat diet. Obese male mice (21-weeks old) were orally dosed with vehicle or CmpdA qd at 10 or 30mg/kg for 10 days; a second vehicle group was paired-fed to 30 mg/kg of CmpdA. Fed blood glucose, body weight and food intake were measured throughout the study. A meal tolerance test (MTT) was conducted on day 10 in fasted mice, including postprandial measurement of total plasma GLP-1, GIP, and PYY.

Results: 1.) CmpdA-10 and 30 mg/kg significantly lowered fed blood glucose on day 6, fasted blood glucose on day 10, and glycemia during MTT. 2.) Pair-fed, 10 and 30 mg/kg of CmpdA lost more total body weight relative to vehicle treated animals (P<0.01); additionally, CmpdA-30mg/kg had significantly more weight loss compared to its matched pair-fed group (PF: -10.5±1.0g vs. CmpdA-30: -15.5±1.0g; P<0.01). 3.) Days 1 through 5, daily food intake was significantly decreased in CmpdA-10 and -30 mg/kg groups vs. vehicle-treated animals (P<0.01), however, the FI difference diminished after day 6. 4.) CmpdA-30mg/kg significantly increased plasma total GLP-1 levels and decreased GIP levels post MTT vs. pair-fed controls. (5) CmpdA significantly decreased epidydimal fat weight at 30 mg/kg and liver weight at 10 mg/kg relative to vehicle controls. Our data suggests that 10-day treatment of a SGLT1/2 inhibitor not only improves glycemic control, but also promotes body weight control in a DIO mouse model.

Supported By: Janssen Research & Development, LLC

1116-P

Effect of Empagliflozin on Heart Failure Outcomes in Subgroups by Age: Results from EMPA-REG Outcome

PEDRO MONTEIRO, NICOLAAS SCHAPER, DOUGLAS CLARK, STEFAN HANTEL, HANS J. WOERLE, SILVIO E. INZUCCHI, DAVID FITCHETT, *Coimbra, Portugal, Maastricht, Netherlands, Ingelheim, Germany, New Haven, CT, Toronto, ON, Canada*

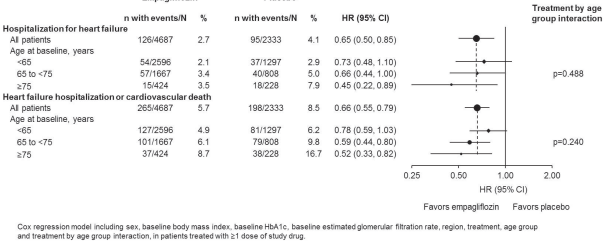
In the EMPA-REG Outcome trial, empagliflozin (EMPA) added to standard of care significantly reduced 3-point major adverse cardiovascular (CV) events, CV death, hospitalization for heart failure, and heart failure hospitalization or CV death (composite) in patients with type 2 diabetes (T2DM) and high CV risk. We investigated the effect of age on reduction in hospitalization for heart failure and heart failure hospitalization or CV death with EMPA.

Patients in EMPA-REG Outcome were randomized to receive EMPA 10 mg, EMPA 25 mg or placebo (PBO). We analyzed hospitalization for heart failure and heart failure hospitalization or CV death in the pooled EMPA group vs. PBO in subgroups by baseline age (<65, 65 to <75, ≥75 years).

A total of 7020 patients were treated. Median observation time was 3.1 years. Mean (SD) age at baseline was 63.2 (8.8) years in the PBO group and 63.1 (8.6) years in the EMPA group. Reductions in hospitalization for heart failure and the composite of heart failure hospitalization or CV death with EMPA vs. PBO were consistent across age categories (Figure). Across age subgroups, reported adverse events were consistent with the known safety profile of EMPA.

EMPA, added to standard of care, reduced the risk of hospitalization for heart failure and heart failure hospitalization or CV death in patients with T2DM and high CV risk irrespective of age.

Figure.



Supported By: Boehringer Ingelheim and Eli Lilly and Company

1117-P

Pioglitazone Does Not Modulate Plasma Sclerostin Levels in Subjects with Impaired Glucose Tolerance (IGT): Results from the ACT NOW Study

JORGE A. VELEZ-GARZA, DANIELE A. GIUSEPPE, RYAN ALONZO, ROBERT MARTINEZ, JAN BRUDER, NICOLAS MUSI, FRANCO FOLLI, RALPH A. DEFRONZO, DEVJIT TRIPATHY, *San Antonio, TX*

Sclerostin has been implicated in the pathogenesis of osteoporosis. Recently elevated sclerostin levels were reported in IGT and T2DM. Given reports of increased fracture risk with thiazolidinediones, we examined the effect of pioglitazone on plasma sclerostin levels and its relationship with insulin sensitivity in subjects with IGT. ACT NOW is a randomized, placebo-controlled study to examine whether pioglitazone (PIO) can prevent/delay development of T2DM. 602 IGT subjects were randomized to PIO (45 mg/day) or placebo (PLAC) and followed for 2.4 years. From the original cohort, we randomly chose 80 subjects; PIO (n=41, 29F/12M, age = 53 ± 1.7 yrs, BMI = 34 ± 0.8 kg/m^2) and PLAC (n=39, 26F/13M, age = 49 ± 1.9 yrs, BMI = 33±0.8 kg/m^2) in whom indices of insulin secretion and insulin sensitivity were

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For author disclosure information, see page A696.

derived from the plasma glucose and insulin concentrations during an OGTT. Plasma sclerostin levels were measured by ELISA. 11 PLAC-treated subjects developed diabetes vs. 2 PIO-treated subjects (p<0.005). There was a marked improvement in insulin sensitivity in PIO treated subjects (6.2±0.4 vs. 4.2±0.6, p<0.005). There were no differences in plasma sclerostin levels between the groups at baseline (38.3± 2 vs. 36.4± 2.5 pmol/l, p=ns) or at study end (36.9 ±2.9 vs. 40.9 ± 4.2 pmol/l, p=ns). Sclerostin inversely correlated with BMI at baseline (r=-0.258, p=0.04) and at study end (r=-0.264, p= 0.03). However, there was no correlation between plasma sclerostin and Matsuda index of insulin sensitivity at baseline (r=-0.01, p=ns) or at study end (r=-0.07, p=ns). Females with IGT had lower sclerostin than males at baseline (33.3± 1.9 vs. 47.4± 4.1pmol/l, p<0.005), as well as at study end (34.6±2.8 vs. 49.4± 4.7pmol/l). Pioglitazone therapy does not affect plasma sclerostin levels. Change in plasma sclerostin are unlikely to play a role in the increased fracture risk and improvement in insulin sensitivity observed with thiazolidinedione therapy.

1118-P

Metformin Attenuates the Increasing Plasma Levels of Fibroblast Growth Factor-21 in Patients with Type 2 Diabetes

XIAOYAN ZHANG, FANG LIU, WOLIN HOU, RUI HE, JUNXI LU, WEIPING JIA, *Shanghai, China*

Objective: Fibroblast growth factor-21 (FGF-21) is an emerging metabolic regulator associated with glucose and lipid metabolism. But type 2 diabetes may be states of relative "FGF-21 resistance." Metformin was widely used as a first-line treatment for patients with type 2 diabetes. We hypothesized that Metformin would influence the increased level of FGF-21.

Design and Methods: We performed a retrospective, observational study of our center's diabetes database and then compared Metformin-treated patients with those not treated with the drug. A multiple stepwise regression analysis was performed to establish whether or not there was an independent relationship between Metformin use and serum FGF-21 level. Serum FGF-21 concentration was determined by enzyme-linked immunosorbent assay.

Results: A total of 477 patients (mean±SD age: 58.37±11.78 years; male/female gender ratio: 1.25:1) were recruited in this study, of whom 174 had been treated with Metformin at least one year. In diabetic men, the serum FGF-21 level in the Metformin group was significantly lower than that in the non-Metformin group [303.11 (182.9-451.12) vs. 342.82 (206.93-593.46) ng/ml, P= 0.003]. However, in diabetic women, there were no significant difference in serum FGF-21 level between the two groups (P>0.05). FGF-21 concentration was positively correlated with triglyceride, fasting C-peptide, γ-glutamyl transpeptidase, but was negatively associated with high-density lipoprotein cholesterol whether in men or women (P<0.05). The multiple stepwise regression analysis showed that the Metformin treatment and triglyceride were the independent risk factors influencing serum FGF-21 level in type 2 diabetic men.

Conclusions: Metformin attenuate the increase in plasma FGF-21 concentrations in type 2 diabetes independently of glycemic effects.

Supported By: National Natural Science Foundation of China

1119-P

Empagliflozin as Add-on to Linagliptin and Metformin in Patients with Type 2 Diabetes (T2DM): Subgroup Analysis by Baseline Demographics in a 24-Week Randomized Trial

JOCHEN SEUFERT, EBRAHIM NADERALI, MARIO MALDONALDO, ANGELO DEL PARIGI, ROBERT TOORAWA, CHRISTOPHER LEE, *Freiburg, Germany, Liverpool, United Kingdom, Ingelheim, Germany, Ridgefield, CT, Bracknell, United Kingdom*

The efficacy and safety of empagliflozin 10 mg and 25 mg vs. placebo as add-on to linagliptin 5 mg and Metformin in patients with T2DM were assessed in a Phase III study. In the open-label period, patients with HbA1c ≥8.0 and ≤10.5% received LINA 5 mg (n=606) as add-on to stable dose Metformin for 16 weeks. Subsequently, patients with HbA1c ≥7.0 and ≤10.5% were randomized to double-blind, double-dummy treatment with a single-pill combination of empagliflozin 10 mg/linagliptin 5 mg (n=112) or empagliflozin 25 mg/linagliptin 5 mg (n=111), or placebo plus linagliptin 5 mg (n=110) for a further 24 weeks. Changes from baseline (randomization) in HbA1c at week 24 were analyzed in subgroups by baseline age, body mass index (BMI), HbA1c, and renal function (estimated glomerular filtration rate [eGFR]).

At week 24, as add-on to linagliptin and Metformin, empagliflozin 10 and 25 mg reduced HbA1c from baseline vs. placebo in all subgroups. Treatment by baseline age, BMI, HbA1c, and eGFR interaction p values were 0.1617, 0.6962, 0.0156, and 0.6992, respectively.

Empagliflozin 10 and 25 mg improved glycemic control vs. placebo as add-on to linagliptin and Metformin for 24 weeks regardless of baseline age, BMI, HbA1c, and eGFR in patients with T2DM.

Table.

		Linagliptin 5 mg and Metformin	
HbA1c (%)	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
Baseline age			
<65 years, n	88	93	95
Change from baseline at week 24, %	0.13 (0.09)	-0.61 (0.09)	-0.60 (0.09)
Difference vs. placebo at week 24 (95% CI)		-0.74 (-1.00, -0.48)	-0.73 (-0.99, -0.47)
p-value		<0.0001	<0.0001
65 to 75 years, n	16	15	13
Change from baseline at week 24, %	0.16 (0.22)	-0.96 (0.23)	-0.28 (0.24)
Difference vs. placebo at week 24 (95% CI)		-1.12 (-1.74, -0.50)	-0.44 (-1.08, 0.19)
p-value		0.0004	0.1714
Baseline BMI			
<25 kg/m², n	24	20	22
Change from baseline at week 24, %	0.07 (0.18)	-0.63 (0.20)	-0.46 (0.19)
Difference vs. placebo at week 24 (95% CI)		-0.70 (-1.23, -0.18)	-0.53 (-1.05, -0.02)
p-value		0.0088	0.0433
25 to <30 kg/m², n	38	30	34
Change from baseline at week 24, %	0.06 (0.15)	-0.44 (0.16)	-0.58 (0.15)
Difference vs. placebo at week 24 (95% CI)		-0.51 (-0.93, -0.08)	-0.64 (-1.05, -0.23)
p-value		0.0195	0.0023
30 to <35 kg/m², n	24	30	34
Change from baseline at week 24, %	0.23 (0.18)	-0.83 (0.16)	-0.65 (0.15)
Difference vs. placebo at week 24 (95% CI)		-1.06 (-1.54, -0.58)	-0.88 (-1.35, -0.42)
p-value		<0.0001	0.0002
≥35 kg/m², n	20	29	20
Change from baseline at week 24, %	0.21 (0.20)	–0.71 (0.16)	–0.50 (0.20)
Difference vs. placebo at week 24 (95% CI)		–0.92 (–1.42, –0.42)	–0.71 (–1.26, –0.16)
p-value		0.0004	0.0113
Baseline HbA1c			
<8.5%, n	76	79	81
Change from baseline at week 24, %	0.19 (0.10)	–0.43 (0.10)	–0.32 (0.10)
Difference vs. placebo at week 24 (95% CI)		–0.62 (–0.89, –0.35)	–0.51 (–0.78, –0.24)
p-value		<0.0001	0.0002
≥8.5%, n	30	30	29
Change from baseline at week 24, %	–0.02 (0.17)	–1.27 (0.16)	–1.26 (0.16)
Difference vs. placebo at week 24 (95% CI)		–1.25 (–1.70, –0.80)	–1.25 (–1.70, –0.79)
p-value		<0.0001	<0.0001
Baseline eGFR			
eGFR ≥90 mL/min/1.73 m², n	56	47	57
Change from baseline at week 24, %	0.04 (0.12)	–0.67 (0.13)	–0.67 (0.12)
Difference vs. placebo at week 24 (95% CI)		-0.71 (-1.05, -0.37)	-0.71 (-1.04, -0.38)
p-value		<0.0001	<0.0001
eGFR 60 to <90 mL/min/1.73 m², n	48	60	52
Change from baseline at week 24, %	0.24 (0.13)	-0.65 (0.11)	-0.48 (0.12)
Difference vs. placebo at week 24 (95% CI)		-0.89 (-1.22, -0.56)	-0.71 (-1.05, -0.37)
p-value		<0.0001	<0.0001

Changes from baseline are adjusted mean (SE) based on MMRM (including respective subgroup, treatment, baseline eGFR [where this is not the subgroup investigated], region, visit, treatment by visit interaction, visit by subgroup interaction, treatment by subgroup interaction, and treatment by visit by subgroup interaction as fixed effects, and baseline HbA1c as a linear covariate [where this is not the subgroup investigated]) in patients who received ≥1 dose of study drug during the double-blind period and had a baseline HbA1c and ≥1 on-treatment value (observed cases, excluding values after initiation of rescue therapy). Differences vs. placebo are adjusted means. n is the number of patients analyzed, which may include patients who did not contribute a value at week 24, but who had earlier values available. eGFR, estimated glomerular filtration rate using Modification of Diet in Renal Disease equation. This study was not powered to detect treatment differences between these baseline demographics.

Supported By: Boehringer Ingelheim and Eli Lilly and Company

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1120-P

Once-Weekly Treatment with Omarigliptin, a DPP-4 Inhibitor, Improves Glycemic Control in Patients Not at Goal on Metformin

R. RAVI SHANKAR, SILVIO E. INZUCCHI, IRA GANTZ, EDWARD A. O'NEILL, VICTORIA SCARABELLO, PAULETTE CEESAY, SHAILAJA SURYAWANSHI, ESENG LAI, *Kenilworth, NJ, New Haven, CT*

Omarigliptin (OMARI) is an oral DPP-4 inhibitor with a half-life that supports once-weekly dosing being developed for treatment of T2DM. In a double-blind, randomized, PBO-controlled trial, subjects (*N*=402) with T2DM and inadequate glycemic control (A1c 7.0 - 10.5%) on Metformin (MET) ≥1500 mg/day were randomized 1:1 to OMARI 25 mg or PBO once weekly. The analyses used a constrained longitudinal data analysis model.

Baseline characteristics were balanced between treatment groups. At week 24, from a mean baseline A1c of 8.1% (OMARI) and 8.0% (PBO), LS Mean (95% CI) changes from baseline in A1c for the OMARI and PBO groups were -0.54% (-0.69, -0.40) and 0.00% (-0.14, 0.15), respectively (difference [Δ] = -0.55% [-0.75, -0.34]; p<0.001). Changes from baseline in 2 hr post-meal glucose (PMG) (mg/dL) were -26.8 (-34.8, -18.7) and -12.2 (-20.7, -3.8), respectively (Δ = -14.5 [-25.6, -3.4]; p=0.011). Changes from baseline in FPG (mg/dL) were -10.7 (-16.0, -5.5) and -1.2 (-6.6, 4.1), respectively (Δ = -9.5 [-16.7, -2.3]; p=0.010). The incidence of subjects with A1c <7% at week 24 was 35.8% and 16.9%, respectively (p<0.001). The incidence of subjects with one or more AEs was 41.3% and 41.3%, with one or more serious AEs was 2.5% and 5.0%, and discontinued due to an AE was 1.0% and 1.0%, respectively. The incidence of subjects with symptomatic hypoglycemia was 3.0% and 2.5% (p=0.760) and with severe hypoglycemia 0.5% and 1.0%, respectively. There were no significant changes in body weight in either group.

In conclusion, in patients with T2DM and inadequate glycemic control on MET, once-weekly OMARI, relative to PBO, provided a clinically meaningful reduction of A1c and a greater proportion of subjects meeting the A1c goal of <7.0%, with concomitant reductions in 2 hr PMG and FPG. Omarigliptin was generally well-tolerated, weight neutral, and had a low incidence of hypoglycemia.

Supported By: Merck & Co., Inc.

1121-P

Effect of Momordica Charantia Administration on Type 2 Diabetes Mellitus, Insulin Sensitivity, and Insulin Secretion

MARISOL CORTEZ-NAVARRETE, ESPERANZA MARTÍNEZ-ABUNDIS, KARINA G. PÉREZ-RUBIO, MANUEL GONZÁLEZ-ORTIZ, *Guadalajara, Mexico*

A decrease in glucose levels, glycated hemoglobin A1c (A1c) and fructosamine has been observed with *Momordica charantia* (MCH) in patients with type 2 diabetes mellitus (T2DM). It is unknown whether the improvement observed is through a modification on insulin secretion, insulin sensitivity, or both. The aim of this study was to evaluate the effect of MCH administration on insulin secretion and insulin sensitivity in patients with T2DM. A randomized, double blind, placebo controlled clinical trial was carried out in 24 adults with newly diagnosed T2DM, without pharmacological treatment. Patients received MCH (1000 mg orally, twice daily) or placebo for 3 months. An oral glucose tolerance test (OGTT) of 2-h was done before and after the intervention. A1c, blood pressure, weight, body mass index (BMI), waist circumference (WC) and fat % were evaluated. Areas under the curve (AUC) of glucose and insulin were calculated. Total insulin secretion (Insulinogenic index), first phase of insulin secretion (Stumvoll index) and insulin sensitivity (Matsuda index) were assessed. Statistical analysis: Wilcoxon and Mann-Whitney U tests. An Ethic Committee approved the protocol and a written informed consent was obtained from all volunteers. In the MCH group, there were significant decreases in weight (79.4±9.2 vs. 78.0±9.2 kg, p=0.007), BMI (29.1±2.4 vs. 28.3±1.9 kg/m^2, p=0.007), fat % (36.7±7.8 vs. 36.3±7.6%, p= 0.021), WC (106±12 vs. 104±11 cm, p=0.013), A1c (7.8±0.8 vs. 7.1±1.3%, p=0.039), 2-h glucose in OGTT (17.1±3.7 vs. 13.2±4.3 mmol/l, p=0.008), and AUC of glucose (61±9 vs. 52 ±13 mmol/l, p=0.047). A significant increase in AUC of insulin (1885±1202 vs. 2174±1422 pmol/l, p=0.093), Insulinogenic index (0.29±0.18 vs. 0.41±0.29, p=0.028) and Stumvoll index (557.8±645.6 vs. 1135.7±725.0, p=0.093) was observed. In conclusion, MCH reduced A1c, 2-h glucose, AUC of glucose, weight, BMI, fat % and WC, with increment in AUC of insulin and in insulin secretion.

1122-P

Efficacy and Safety of Saxagliptin Add-on to Metformin Compared with Acarbose Add-on to Metformin in Patients with Type 2 Diabetes Mellitus (T2DM) Inadequately Controlled with Metformin Monotherapy

JIN DU, LI LIANG, HUI FANG, FENGMEI XU, WEI LI, LIYA SHEN, YIMING MU, *Beijing, China, Shenyang, China, Tangshan, China, Hebi, China, Xuzhou, China, Wuhan, China*

This is a multicentre, randomized, open-label, parallel group, active controlled Phase IV study to assess the efficacy, safety and tolerability of saxagliptin plus Metformin combination therapy compared with acarbose plus Metformin in patients with type 2 diabetes mellitus (T2DM) who are inadequately controlled with Metformin monotherapy over 24 weeks. Patients were randomized to saxagliptin (5mg daily, given as once daily, n=238) add on to Metformin or acarbose (up to 300mg daily, given as three equally divided doses, n=243) add-on to Metformin. 12-week results show that saxagliptin add-on to Metformin is significant superior to acarbose add-on to Metformin in HbA1c (-0.78% vs. -0.61%, p=0.0410) and in fasting plasma glucose (-1.06 mmol/L vs. -0.63 mmol/L, p=0.0086). 24-week results show that saxagliptin add-on to Metformin is non-inferior to acarbose add-on to Metformin in glycaemic control in HbA1c (-0.81% vs. -0.76%, p=0.6323), fasting plasma glucose (-0.99 mmol/L vs. -1.01 mmol/L, p=0.8909), and 120 min postprandial glucose (-0.76 mmol/L vs. -1.15 mmol/L, p=0.1169), respectively. The proportion of patients experiencing gastrointestinal (GI) adverse events (AEs) were significantly more frequent with acarbose plus Metformin than saxagliptin plus Metformin (24.7% vs. 5.5%, P< 0.0001). The proportion of hypoglycaemia was similar for both groups (1.2% for saxagliptin plus Metformin and 1.6% for acarbose plus Metformin), no severe hypoglycaemia was reported for either group. In conclusion, saxagliptin add-on to Metformin is non-inferior to acarbose add-on to Metformin in glycaemic control but with better GI tolerability in T2DM patients who have failed initial Metformin therapy. The findings from this study will add further clinical evidence to physicians for selection of second line treatments for T2DM patients failed on Metformin monotherapy.

Supported By: AstraZeneca

1123-P

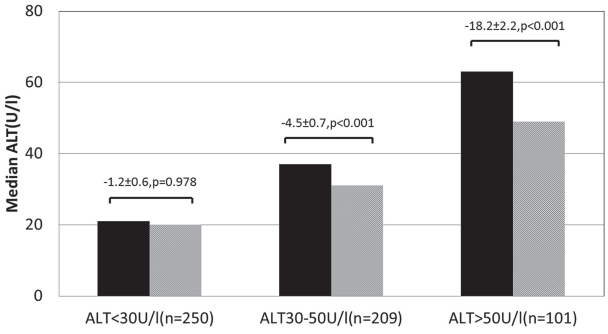
Does Dapagliflozin Affect the Metabolic Response in Patients with Elevated Alanine Aminotransferase (ALT) and Type 2 Diabetes? The Association of British Clinical Diabetologists Nationwide Dapagliflozin Audit

MAHENDER YADAGIRI, PIYA SEN GUPTA, MELISSA L. CULL, DAVID PRICE, VICTOR OGUNTOLU, KOMAL IMTIAZ, DENIS BARNES, AILISH NUGENT, ANTHONY ROBINSON, IAN W. GALLEN, KAREN A. ADAMSON, ROBERT E.J. RYDER, *Birmingham, United Kingdom, Swansea, United Kingdom, Wolverhampton, United Kingdom, Chorley, United Kingdom, Tunbridge Wells, United Kingdom, Belfast, United Kingdom, Bath, United Kingdom, Reading, United Kingdom*

We evaluated the effect of: (1) dapagliflozin on metabolic response in patients with elevated ALT and (2) baseline ALT on metabolic response to dapagliflozin. Data was obtained from our audit of dapagliflozin in real-clinical use 2014-2015 (n=1725). Inclusion criteria for analysis: baseline and follow up ALT. Patients were categorized into 3 groups (ALT<30; ALT30-50; ALT>50U/l). Of 558 patients [age 57.7±9.9 years, 57.8% males, type 2 diabetes duration 10.0 (5.0-16.0) years, baseline ALT 31.0 (22.0-42.2) U/l, weight 98.7 (86.0-114.9) kg, BMI 34.7 (30.7-39.6) kg/m^2 and HbA1c 9.3 (8.4-10.3)%, over 6.0 (4.0-9.0) months], median reduction in ALT was 4.0 (2.0-4.2) U/l, p<0.001, weight 2.8 (1.7-2.6) kg, p<0.001and HbA1c 1.0 (0.1-0.9)%, p<0.001. Comparing groups, ALT fell with higher but not lower ALT (Figure). Baseline ALT correlated with ALT fall (R=0.5, p<0.01), weakly with HbA1c fall (R=0.1, p<0.05) and did not correlate with weight fall.

Apart from positive impact on glycemic control and weight, dapagliflozin has a clinically and statistically significant response on ALT reduction in patients with type 2 diabetes with a high baseline ALT≥30U/l. This result may have implications regarding the insulin resistance associated with fatty liver and with nonalcoholic fatty liver disease.

Figure. Baseline (Black) and First Return (Grey) ALT U/l, Mean (±SE) Reduction in 3 Groups.



Comparing groups [baseline ALT<30U/l, n=250 (44.8%); ALT 30-50U/l, n=209(37.1%); ALT>50U/l, n=101(18.1%)], ALT changed from 21.0(17.0-25.0) [median(interquartile range)] to 20.0(16.0-26.0)U/l (p=0.978), 37.0(33.0-41.0) to 31.0 (26.0-38.0)U/l (p<0.001) and 68.0(57.0-73.5) to 49.0 (37.0-60.0)U/l (p<0.001) respectively.

Supported By: Association of British Clinical Diabetologists

1124-P

DS-8500a, a Novel Orally Available GPR119 Agonist Improves Glucose Tolerance in Type 2 Diabetic Rats

KOJI MATSUMOTO, TOMOMI YOSHITOMI, KANAKO TAKAHASHI, NAOMI TANAKA, HIDENORI NAMIKI, TOMOKO ISHIZUKA, KATSUYOSHI CHIBA, MUTSUMI KUROHA, TAKASHI SHIMADA, *Tokyo, Japan*

G-protein coupled receptor 119 (GPR119) has been shown to be highly expressed in small intestinal L-cells and pancreatic beta-cells, and mediate intracellular cAMP concentration, glucagon like peptide (GLP-1) secretion, and glucose-stimulated insulin secretion (GSIS). DS-8500a is a GPR119 agonist under investigation for the treatment of T2DM. This study evaluated the basic pharmacological activities of DS-8500a based on the proposed GPR119 agonism. DS-8500a increased intracellular cAMP in human, rat, and mouse GPR119 expressing CHO-K1 cells in a concentration-dependent manner with EC_{50} of 51.5, 98.4, and 108.1 nmol/L, respectively. In addition, DS-8500a had a higher intrinsic activity of the production of intracellular cAMP in human GPR119 expressing CHO-K1 cells than those of other GPR119 agonists studied. DS-8500a had no significant effect on multiple receptors, channels, or transporters studied (66 items, IC_{50}: >10 μmol/L). In Sprague-dawley rats, DS-8500a (0.1 to 10 mg/kg, oral) significantly enhanced GSIS in a dose-dependent manner ($P < 0.05$, vs. vehicle). Unlike Nateglinide, Glimepiride and Glibenclamide, DS-8500a (10 mg/kg, oral) did not cause a reduction in the plasma glucose levels in fasting condition. In Zucker fatty rats, DS-8500a (3 mg/kg, oral) significantly elevated plasma total GLP-1 concentration continuously up to 3.5 h post-dose compared with control ($P < 0.05$), and dose-dependently improved glucose tolerance compared with control (1 to 10 mg/kg, $P < 0.0001$). Plasma glucose AUC during oGTT was 497±16 mg·h/dL and 633±15 mg·h/dL in DS-8500a (3 mg/kg) and vehicle treated group, respectively. In conclusion, DS-8500a is a selective, potent and orally available GPR119 agonist. In mechanistic studies, DS-8500a enhanced GSIS and promoted GLP-1 secretion. In a pharmacodynamic study, DS-8500a improved glucose intolerance. These results suggest that DS-8500a could provide a new strategy for glycemic control in patients with T2DM.

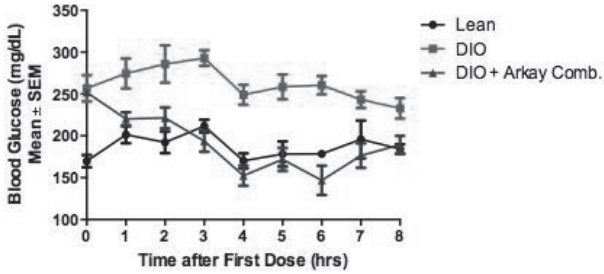
1125-P

Anti-inflammatory Centric Drug Combination Lowers Nonfasting Blood Glucose Levels in C57BL/6 DIO Mice with Insulin Resistance

RAVI KUMAR, *East Windsor, NJ*

The progressive deterioration of metabolic control of glucose homeostasis that occurs in spite of intense therapies with the modalities used is indicative of progressive deterioration and severity of inflammation-triggered pancreatic beta cell dysfunction. Deteriorating pancreatic beta cell dysfunction disrupts tight regulation of hepatic gluconeogenesis by opposing actions of insulin and glucagon. ARKAY Therapeutics is filling the gap that exists in the modalities by targeting immune modulation-inflammation-insulin resistance axis. ARKAY Therapeutics is advancing a proprietary anti-inflammatory centric product concept to treat patient-specific comorbidities and more importantly, achieve long term sustainable glycemic control by correcting pancreatic islet dysfunction. C57BL/6 DIO mice (Jackson Labs) were fed HFD for 16 weeks to induce hepatic insulin resistance due to impaired insulin sensitivity for hepatic gluconeogenesis as well as post-prandial hyperglycemia due to beta cell dysfunction. A Preliminary POC (proof-of-concept data) shows that our lead anti-inflammatory centric combination of Celecoxib, Metformin and Valsartan counteracts elevated non-fasting blood glucose levels in C57BL/6 DIO male mice treated with the vehicle and Metformin respectively by correcting pancreatic islet cell dysfunction and by restoring insulin sufficiency.

Figure. Day 1 ARKAY Pilot Study.



1126-P

Ranolazine Reduces Oxidative Stress and Inflammation in C2C12 Skeletal Muscle Cells

ILEANA TERRUZZI, PAMELA SENESI, ANNA MONTESANO, FERNANDA VACANTE, LIVIO LUZI, *Milan, Italy, San Donato Milanese, Italy*

Ranolazine (RAN), an antianginal drug, acts blocking the cardiac late component of the voltage-dependent sodium current. Recent clinical evidence of beneficial effects of RAN in reducing glycosylated hemoglobin in type 2 diabetic patients raises interest on its role in insulin target tissues. Whilst its action on the heart was studied extensively, few studies have focused on RAN action on skeletal muscle differentiation and inflammation process in insulin resistance states. Building on previous data of ours indicating that RAN could be able to improve skeletal muscle differentiation and myotubes formation (1088-P, 74th ADA congress, 2014), we analyzed the molecular mechanisms underlying RAN effects on oxidative stress and inflammatory state utilizing C2C12 murine myoblastic cell line. 10μM RAN was added to C2C12 during proliferation, differentiation and in neo-formed myotubes. $Ca^{(2+)}$/calmodulin-dependent kinases (CaMK) II protein expression was determined by Western Blot and Immunofluorescence assay and we showed that RAN improved CaMKII signaling. RAN plays an important role regulating calcium intracellular fluxes, mitochondrial activity and oxidative stress. To elucidate RAN action on mitochondrial activity, specific mitochondrial immunostaining (MITO) was performed: RAN decreases MITO signal. Osteopontin (OPN) is a new important link between inflammation and myogenesis during regeneration of injured skeletal muscles. In all phases of differentiation OPN protein expression was studied. Immunofluorescence assay revealed that RAN decreases OPN level in the late phase of differentiation. In summary, our data indicated how RAN could improve oxidative stress and inflammatory response, modulating mitochondrial activity and inhibiting OPN expression and support the role of RAN in skeletal muscle differentiation. In conclusion, RAN could have an anti-inflammatory action in the skeletal muscle.

1127-P

Impact of Changes in Glucose-Lowering Therapy on Analyses of Glycemic Control and Weight in EMPA-REG Outcome

GUNTRAM SCHERNTHANER, ANDRE SCHEEN, EBRAHIM NADERALI, ODD ERIK JOHANSEN, MICHAELA MATTHEUS, BERNARD ZINMAN, *Vienna, Austria, Liège, Belgium, Liverpool, United Kingdom, Asker, Norway, Ingelheim, Germany, Toronto, ON, Canada*

We present changes in glycemic control and weight with empagliflozin (EMPA) vs. placebo (PBO) in EMPA-REG Outcome based on two approaches, addressing the impact of additional glucose-lowering therapies introduced during the trial.

Patients with type 2 diabetes and high cardiovascular risk were randomized to receive EMPA 10 mg or 25 mg or PBO in addition to standard of care. Background glucose-lowering therapy was to remain unchanged for 12 weeks then could be adjusted according to local guidelines. We compared changes in HbA1c, fasting plasma glucose (FPG) and weight in all patients prior to receiving additional glucose-lowering therapy or changes in background glucose-lowering therapy vs. all data obtained in all patients who were randomized and received at least one dose of study drug (modified intent-to-treat [ITT] approach).

Of 7020 treated patients, 54.2% and 32.5% in the PBO and EMPA groups, respectively, received additional or intensified glucose-lowering therapy. At week 12, comparable differences in HbA1c, FPG and weight were seen

For author disclosure information, see page A696.

(Table). However, interestingly, at week 164 there were only slight differences between the 2 approaches despite having the option to change glucose-lowering therapy.

In EMPA-REG Outcome, there were no clinically meaningful differences between analyses of glycemic control and weight that included or excluded changes in glucose-lowering therapy.

Table.

		ITT			Glucose-lowering therapy unchanged*		
		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA1c (%)	Baseline, n analyzed patients	2294	2296	2296	1994	2025	2001
	Baseline	8.08 (0.02)	8.08 (0.02)	8.07 (0.02)	8.06 (0.02)	8.07 (0.02)	8.05 (0.02)
	Week 12, n analyzed patients	2272	2272	2280	1982	2006	1998
	Change from baseline at week 12	–0.11 (0.02)	–0.65 (0.02)	–0.71 (0.02)	–0.10 (0.02)	–0.63 (0.02)	–0.70 (0.02)
	Week 164, n analyzed patients	962	1006	1043	235	380	432
	Change from baseline at week 164	0.03 (0.03)	–0.29 (0.03)	–0.40 (0.03)	0.26 (0.05)	–0.27 (0.04)	–0.42 (0.04)
FPG (mg/dL)	Baseline, n analyzed patients	2309	2311	2311	2230	2236	2229
	Baseline	153.5 (0.9)	153.2 (0.9)	151.8 (0.9)	153.7 (0.9)	153.5 (0.9)	151.7 (0.9)
	Week 12, n analyzed patients	2226	2228	2234	1941	1963	1953
	Change from baseline at week 12	5.2 (0.8)	–15.2 (0.8)	–18.6 (0.8)	5.4 (0.8)	–15.6 (0.8)	–19.3 (0.8)
	Week 164, n analyzed patients	965	1012	1053	235	380	430
	Change from baseline at week 164	4.7 (1.4)	–3.6 (1.4)	–9.3 (1.3)	10.8 (2.2)	–6.5 (1.8)	–12.9 (1.7)
Weight (kg)	Baseline, n analyzed patients	2285	2290	2283	1918	1980	1942
	Baseline	86.7 (0.4)	86.0 (0.4)	86.5 (0.4)	86.6 (0.4)	85.7 (0.4)	86.6 (0.4)
	Week 12, n analyzed patients	1915	1893	1891	1651	1658	1642
	Change from baseline at week 12	–0.2 (0.1)	–1.4 (0.1)	–1.7 (0.1)	–0.2 (0.1)	–1.4 (0.1)	–1.6 (0.1)
	Week 164, n analyzed patients	1239	1298	1335	280	456	501
	Change from baseline at week 164	–0.8 (0.1)	–2.4 (0.1)	–2.7 (0.1)	–0.6 (0. 2)	–2.4 (0.2)	–3.1 (0.2)

Baseline: mean (SE); changes from baseline: adjusted mean (SE) based on mixed model repeated measures analysis. p<0.001 for all differences in change from baseline with empagliflozin vs. placebo. *Patients who did not receive additional glucose-lowering therapy or who did not have changes in background glucose-lowering therapy.

Supported By: Boehringer Ingelheim and Eli Lilly and Company

1128-P

Empagliflozin (EMPA) as Add-on to Linagliptin (LINA) and Metformin in Patients with Type 2 Diabetes (T2DM): A 24-Week Randomized, Double-Blind, Double-Dummy, Parallel-Group Trial

EIRIK SØFTELAND, JURIS J. MEIER, BENTE VANGEN, ROBERT TOORAWA, MARIO MALDONADO, HANS J. WOERLE, ULI C. BROEDL, *Bergen, Norway, Bochum, Germany, Asker, Norway, Bracknell, United Kingdom, Ingelheim, Germany*

This Phase III study investigated the efficacy and safety of EMPA 10 mg and 25 mg vs. placebo (PBO) as add-on to LINA 5 mg and Metformin in patients with T2DM.

Patients with HbA1c ≥8.0 and ≤10.5% while receiving stable-dose Metformin were treated with open-label LINA 5 mg (n=606) for 16 weeks. Subsequently, those with HbA1c ≥7.0 and ≤10.5% were randomized to double-blind, double-dummy treatment with a single-pill combination of EMPA 10 mg/LINA 5 mg (n=112) or EMPA 25 mg/LINA 5 mg (n=111), or PBO plus LINA 5 mg (n=110) for 24 weeks. Endpoints included changes from baseline (randomization) in HbA1c (primary endpoint), fasting plasma glucose (FPG), and weight (key secondary endpoints) after 24 weeks of double-blind treatment.

At week 24, EMPA 10 mg and 25 mg significantly reduced HbA1c, FPG, and weight from baseline compared with PBO as add-on to LINA 5 mg and Metformin (Table). Greater proportions of patients reached HbA1c <7% at week 24 with EMPA 10 mg (37.0%) and 25 mg (32.7%) than PBO (17.0%; odds ratio [95% CI] vs. placebo: 4.0 [1.9, 8.7] and 2.9 [1.3, 6.1], respectively; both p<0.01). Open-label LINA 5 mg reduced HbA1c by -1.16 (SD 1.10)%. Adverse events are presented in the Table.

EMPA 10 mg and 25 mg improved glycemic control and weight vs. PBO as add-on to LINA 5 mg and Metformin for 24 weeks and were well tolerated in patients with T2DM.

Table.

	Linagliptin 5 mg and Metformin		
	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA1c (%)			
Baseline	7.96 (0.08)	7.97 (0.08)	7.97 (0.08)
Change from baseline at week 24	0.14 (0.09)	-0.65 (0.08)	-0.56 (0.08)
Difference vs. PBO at week 24		-0.79	-0.70
(95% CI)		(-1.02, -0.55)	(-0.93, -0.46)
p-value		<0.0001	<0.0001
FPG (mmol/L)			
Baseline	9.0 (0.2)	9.3 (0.2)	9.4 (0.2)
Change from baseline at week 24	0.3 (0.2)	-1.5 (0.2)	-1.8 (0.2)
Difference vs. PBO at week 24		-1.8	-2.1
(95% CI)		(-2.3, –1.3)	(–2.6, –1.6)
p-value		<0.0001	<0.0001
Weight (kg)			
Baseline	82.3 (1.9)	88.4 (2.0)	84.4 (1.8)
Change from baseline at week 24	–0.3 (0.3)	–3.1 (0.2)	–2.5 (0.2)
Difference vs. PBO at week 24		–2.8	–2.2
(95% CI)		(–3.5, –2.1)	(–2.9, –1.5)
p-value		<0.0001	<0.0001
Adverse events, n (%) *			
Any adverse event	75 (68.2)	62 (55.4)	57 (51.8)
Confirmed hypoglycemia†	1 (0.9)	0	3 (2.7)
Events requiring assistance	0	0	1 (0.9)
Events consistent with urinary tract infection‡	8 (7.3)	8 (7.1)	4 (3.6)
Events consistent with genital infection§	2 (1.8)	2 (1.8)	5 (4.5)

Baseline values are mean (SE). Changes are adjusted mean (SE) based on MMRM (including treatment, baseline estimated glomerular filtration rate, region, visit, and visit by treatment as fixed effects and baseline values for HbA1c and the endpoint in question as linear covariates) in patients who received ≥1 dose of study drug during the double-blind period and had a baseline HbA1c and ≥1 on-treatment value (observed cases, excluding values after initiation of rescue therapy). *Patients who received ≥1 dose of study drug during the double-blind period (n=110 for placebo, n=112 for empagliflozin 10 mg, n=110 for empagliflozin 25 mg). †Plasma glucose ≤70 mg/dL and/or requiring assistance. ‡Based on 79 MedDRA preferred terms. §Based on 138 MedDRA preferred terms. MedDRA v. 17.1.

Supported By: Boehringer Ingelheim and Eli Lilly and Company

1129-P

WITHDRAWN

1130-P

Quality Measures Assessment of Triple Therapy with Saxagliptin (SAXA) + Dapagliflozin (DAPA) + Metformin (MET) in Type 2 Diabetes Mellitus (T2D) Patients with Inadequate Response to DAPA + MET or SAXA + MET

LAWRENCE BLONDE, CHANTAL MATHIEU, JOHN J. SHEEHAN, STEPHAN MATTHAEI, *New Orleans, LA, Leuven, Belgium, Gaithersburg, MD, Quakenbrück, Germany*

In 2 phase 3 trials, therapy with SAXA + DAPA + MET significantly improved A1c at week 24 vs. placebo (PBO) added to MET + either drug alone. In Study 1, adults with T2D inadequately responding to SAXA (5 mg/d) + MET (≥1500 mg/d) were randomized to DAPA (10 mg/d) or PBO. In Study 2, patients inadequately responding to DAPA + MET were randomized to SAXA or PBO. These post hoc evaluations used evidence-based and vetted measures of diabetes care from the National Quality Forum (NQF): Comprehensive Diabetes Care (A1c <8% or >9% [poor control; a Centers for Medicare and Medicaid Services Star Measure], SBP/DBP <140/90 mm Hg) of the Healthcare Effectiveness Data and Information Set (HEDIS), and Optimal Diabetes Care (A1c <8%, SBP/DBP <140/90 mm Hg) of the Physician Quality Reporting System.

At week 24 in Study 1, significantly more patients on triple therapy achieved most quality measures vs. SAXA + MET dual therapy. In Study 2, although most measures were numerically better, improvement with triple therapy was generally not statistically different.

These findings show that at 24 weeks, more patients achieve quality measures with triple therapy (SAXA + DAPA + MET) as opposed to dual therapy with either SAXA + MET or DAPA + MET, although the effect may be more pronounced when DAPA is added to SAXA + MET than when SAXA is added to DAPA + MET.

Table.

Parameter	Study 1		Study 2	
	SAXA + MET n=160	SAXA + DAPA + MET n=160	DAPA + MET n=162	SAXA + DAPA + MET n=153
A1c <7%	13.3%	36.7%	24.4%	34.0%
	P<0.001		P=0.062	
A1c <8%	48.1%	74.7%	65.0%	72.7%
	P<0.001		P=0.147	
SBP <140 mm Hg and DBP <90 mm Hg	72.8%	79.7%	82.5%	80.9%
	P=0.186		P=0.719	
A1c <7%, SBP <140 mm Hg, and DBP <90 mm Hg	9.5%	30.4%	20.0%	26.0%
	P<0.001		P=0.210	
A1c <8%, SBP <140 mm Hg, and DBP <90 mm Hg	33.5%	59.5%	52.5%	59.3%
	P<0.001		P=0.227	
A1c >9%	20.9%	5.1%	11.9%	4.0%
	P<0.001		P=0.011	

1131-P

Network Meta-analysis of DPP-4i/SGLT2i Combination as Add-on to Metformin for T2DM

MICHELLE ELAINE ORME, LEI QIN, NEBIBE VAROL, KELLY BELL, JAYANTI MUKHERJEE, *Swindon, United Kingdom, Gaithersburg, MD, Cambridge, United Kingdom, Fort Washington, PA, Wallingford, CT*

We updated a network meta-analysis (presented June 2015) to compare the combination dipeptidyl peptidase-4 inhibitors/sodium glucose co-transporter-2 inhibitors (DPP-4i/SGLT2i), against DPP-4i and SGLT2i alone, or glucagon-like peptide-1 receptor agonists (GLP-1RA), thiazolidinediones (TZD), or sulfonylureas (SU) in type 2 diabetes mellitus (T2DM) patients poorly controlled on Metformin alone. Across the 44 studies included in the 24 (+/- 6) week base case analysis, the average patient age was 56 years, duration of diabetes 6.4 years, baseline HbA1c 8.1%, weight 86 kg and 48% were female. Based on the random-effects model adjusted for baseline HbA1c, DPP-4i/SGLT2i, when added to Metformin, results in significantly lower HbA1c than DPP-4i, SGLT2i, TZD, SU and placebo. DPP-4i/SGLT2i combination provides statistically significant benefits in terms of weight loss when compared with DPP-4i, TZD, SU or placebo. DPP-4i/SGLT2i results in a significant reduction in systolic blood pressure compared with placebo and SU. The odds of hypoglycemia for the DPP-4i/SGLT2i combination are not significantly different from placebo, SGLT2i or DPP-4i alone, GLP-1RA or TZD but are significantly lower than SU. The results indicate that the addition of DPP-4i/SGLT2i to Metformin will provide improved glycemic control and beneficial blood pressure and weight effects, without increasing hypoglycemia risk.

Table. Basecase Random-effects Network Meta-analysis at 24 ± 6 Weeks: DPP-4i/SGLT2i/MET Compared with Other Drug Classes + MET for T2D Patients Inadequately Controlled on MET Alone.

DPP-4i/SGLT-2i/MET compared with	Difference in HbA1c, %‡
SGLT-2i/MET	-0.44 (-0.66, -0.22)†
GLP-1RA/MET	-0.26 (-0.52, 0.01)
DPP-4i/MET	-0.49 (-0.72, -0.26)†
TZD/MET	-0.33 (-0.60, -0.04)†
SU/MET	-0.32 (-0.59, -0.05)†
placebo/MET	-1.13 (-1.37, -0.89)†
baseline	-1.21 (-1.46, -0.96)†
DPP-4i/SGLT-2i/MET compared with	Difference in weight, kg
SGLT-2i/MET	0.10 (-0.50, 0.71)
GLP-1RA/MET	-0.42 (-1.12, 0.30)
DPP-4i/MET	-2.04 (-2.68, -1.41)†
TZD/MET	-4.27 (-5.00, -3.55)†
SU/MET	-4.09 (-4.82, -3.35)†
placebo/MET	-1.81 (-2.45, -1.17)†
baseline	-2.70 (-3.36, -2.03)†
DPP-4i/SGLT-2i/MET compared with	Difference in SBP, mmHg
SGLT-2i/MET	1.10 (-1.47, 3.72)
GLP-1RA/MET	-2.02 (-4.67, 0.76)
DPP-4i/MET	-1.92 (-4.51, 0.69)
TZD/MET	-2.13 (-5.55, 1.37)
SU/MET	-5.17 (-8.05, -2.18)†
placebo/MET	-3.55 (-6.18, -0.89)†
baseline	-3.44 (-6.35, -0.57)†
DPP-4i/SGLT-2i/MET compared with	OR of hypoglycemia†
SGLT-2i/MET	0.78 (0.22, 2.51)
GLP-1RA/MET	0.58 (0.13, 2.32)
DPP-4i/MET	0.91 (0.25, 3.21)
TZD/MET	1.86 (0.37, 8.79)
SU/MET	0.15 (0.03, 0.70)†
placebo/MET	0.88 (0.24, 3.15)
DPP-4i/SGLT-2i/MET absolute risk	1.9% (0.5%, 6.75%)

Median (95% credible interval); † statistically significant result based on 95% credible interval; ‡ adjusted for baseline HbA1c%; †symptomatic or reported; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; MET, metformin; NMA, network meta-analysis; OR, odds ratio; RE, random-effects; SAXA, saxagliptin; SBP, systolic blood pressure; SGLT-2i, sodium glucose transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione

1132-P

Comparison of Effects of Teneligliptin vs. Sitagliptin on Oxidative Stress and Endothelial Function in Type 2 Diabetes Patients with Chronic Kidney Disease

KAZUNORI YANAGI, KUNIHIRO SUZUKI, CHIE AOKI, TERUO JOJIMA, TOSHIE IJIMA, YOSHIMASA ASO, *Mibu, Japan*

Objective: The aim of the present study was to investigate the effects of teneligliptin or sitagliptin on oxidative stress and endothelial function in Japanese type 2 diabetes patients with chronic kidney disease (CKD).

Subjects and Methods: Forty-five type 2 diabetes patients with CKD who received sitagliptin for at least 12 months were randomized to either continuation of sitagliptin (n = 23) or switching to teneligliptin (n = 22) for 6 months. The parameters were evaluated at baseline and 6 months after the treatment with continued sitaglipitin or teneligliptin as follows; blood pressure, hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), urinary albumin excretion, endothelial function evaluated by reactive hyperemia index (RHI; EndoPAT® system), reactive oxygen metabolites (ROMs) measured by the d-ROMS test, 8-hydroxy-2′-deoxyguanosine (8-OHdG), liver-type fatty acid binding protein (L-FABP), and urinary 8- isoprostane.

Results: There were no significant differences between the two groups with regard to age, male-to-female ratio, duration of diabetes, body mass index, HbA1c, eGFR, or urinary albumin excretion levels at baseline. We found no significant differences in changes of HbA1c, eGFR, or urinary albumin excretion levels between the two groups after 6 month-treatment. However, treatment with teneligliptin, but not sitagliptin, significantly improved RHI, and decreased the change in d-ROMs, 8-OHdG, L-FABP and 8- isoprostane.

Conclusions: The present study demonstrated that teneligliptin, but not sitagliptin, can improve endothelial function and reduce renal and vascular oxidative stress with type 2 diabetes patients with CKD, independently of reducing albuminuria or improving glycemic control.

For author disclosure information, see page A696.

1133-P

Study of Saroglitazar in Treatment of Prediabetes with Dyslipidemia

DEEPAK BHOSLE, VANDANA BHOSLE, JYOTI BOBDE, ABHIJEET BHAGAT, RAJESH KADAM, *Aurangabad, India*

Saroglitazar, a dual PPAR α/γ agonist, is approved in India for the treatment of diabetic dyslipidemia and type 2 diabetes with hypertriglyceridemia not controlled with statin. This is an observational, single centre study, conducted in patients with prediabetes and dyslipidemia to evaluate the safety and efficacy of saroglitazar. Subjects with baseline HbA1c 5.7-6.4% and dyslipidemia as per NCEP criteria were enrolled in this study. Subjects with on-going medications affecting blood glucose or lipids were excluded from the study. Total 40 patients (28 male participants) with mean age of 48.15 years were enrolled in the study. The mean baseline HbA1c and triglycerides were 6.3% and 348 mg/dL respectively. All subjects were given saroglitazar 4mg once daily for 24 weeks. The change in lipid parameters, HbA1c, liver enzymes, and kidney functions were evaluated at 24 weeks by using paired t-test. At 24 weeks, there were significant improvements in HbA1c level and lipid parameters (Table). There was no adverse effect of saroglitazar on liver enzymes or kidney function at week 24. One patient reported with an episode of diarrhea which was resolved with antimicrobials without interrupting study medication. This is the first data of saroglitazar in patients with prediabetes and dyslipidemia. The results indicate that saroglitazar is safe and well tolerated, and can be effectively used for the treatment of prediabetes with dyslipidemia.

Table. Change in Laboratory Parameters after 24 Weeks Treatment with Saroglitazar.

Laboratory parameters	Baseline (n=40)	24 weeks follow-up (n=40)	Absolute change from baseline	% change from baseline	P-value
Triglycerides (mg/dL)	348.0 ± 86.98	216.4 ± 72.34	-131.5 ± 48.64	-38.7 ± 10.72	<0.0001
LDL-C (mg/dL)	209.8 ± 47.67	177.9 ± 47.56	-31.9 ± 14.22	-15.7 ± 8.47	<0.0001
HDL-C (mg/dL)	44.8 ± 5.71	49.0 ± 6.13	4.2 ± 2.39	9.6 ± 5.54	<0.0001
Non HDL-C (mg/dL)	278.6 ± 42.38	224.1 ± 47.15	-54.5 ± 25.11	-19.9 ± 10.35	<0.0001
HbA1c (%)	6.3 ± 0.16	5.5 ± 0.30	-0.7 ± 0.25	-	<0.0001
Alanine aminotransferase (U/L)	26.9 ± 6.16	24.6 ± 6.61	-2.3 ± 6.12	-6.7 ± 23.14	0.024
Serum creatinine (mg/dL)	1.0 ± 0.17	1.0 ± 0.14	0.0 ± 0.18	6.1 ± 19.46	0.21

All values are mean ± SD.

1134-P

Mixed Meal Test Reveals the HbA1c-Lowering Effect of DPP-4 Inhibitors via Free Fatty Acid and Glucagon

KENTARO SAKAMOTO, SUMIE OKAHATA, TAKAKO MITSUMATSU, TERUO SHIBA, *Tokyo, Japan*

Purpose: To evaluate the effect of DPP-4 inhibitors and elucidate the mechanisms through which to attain HbA1c reduction on the focus of free fatty acids.

Methods: We performed mixed meal tests for patients initiating DPP-4 inhibitor use before and after 1 month administration. We checked plasma glucose (PG), insulin (IRI), CPR, glucagon (IRG), and free fatty acids (FFA).

Results: 66 patients (39 men and 27 women; mean age 63.1 years and HbA1c 8.15±1.51%) were analyzed. The breakdown of DPP-4 inhibitors was 32 of sitagliptin, 13 of vildagliptin, 13 of linagliptin, 5 of teneligliptin, and 3 of anagliptin. By 1 month of administration, HbA1c reduced to 7.22±0.73%. MMTs showed significant reduction of PG, and FFA at each time point (except for FFA at 60 min), and so did the AUCs. Whereas IRI and CPR exhibited no significant differences, IRG significantly reduced at 30, 60, and 120 minutes respectively, and so did the AUC. On the parameters at fasting, difference (Δ) in FFA showed no significant correlations to ΔPG, ΔIRI, ΔCPR, ΔIRG, ΔIRG/IRI nor changes in indices of insulin resistance such asΔHOMA-IR and ΔISI (Matsuda Index), but positive correlation to ΔHbA1c. ΔPG positively correlated to ΔIRI or ΔCPR, suggesting the secondary change in insulin secretion. The reduction in HbA1c showed significant correlation toΔAUC of FFA and IRG/IRI, but not of IRI, CPR, IRG. ΔAUC of FFA correlated positively to that of IRG, but not PG, IRI, nor IRG/IRI. It also showed a positive correlation to BMI.

Discussion and Conclusion: While FFA reduction did not exhibit definite correlation to the change in insulin resistance, it correlated to HbA1c improvement. There is a possibility that HbA1c improvement caused by DPP-4 inhibitors is brought through FFA reduction driven by IRG change.

1135-P

Linagliptin (LINA) as Add-on to Empagliflozin (EMPA) and Metformin in Patients with Type 2 Diabetes (T2DM): Subgroup Analysis by Baseline Demographics in Two 24-Week Randomized, Double-Blind, Parallel-Group Trials

SANJA GILJANOVIC KÎS, KAMLESH KHUNTI, MARIO MALDONALDO, ANGELO DEL PARIGI, SOPHIA GÖTZ, CHRISTOPHER LEE, *Zagreb, Croatia, Leicester, United Kingdom, Ingelheim, Germany, Ridgefield, CT, Biberach, Germany*

The efficacy and safety of LINA 5 mg vs. placebo (PBO) as add-on to EMPA 10 mg or EMPA 25 mg and Metformin in patients with T2DM were assessed in two Phase III studies. Patients with HbA1c ≥8.0 and ≤10.5% while receiving stable-dose Metformin received open-label EMPA 10 mg (study 1; n=352) or EMPA 25 mg (study 2; n=354) for 16 weeks. Subsequently, patients with HbA1c ≥7.0 and ≤10.5% were randomized to 24 weeks' double-blind, double-dummy treatment with a single-pill combination of LINA 5 mg/EMPA 10 mg (n=126) or PBO + EMPA 10 mg (n=130) in study 1, and a single-pill combination of LINA 5 mg/EMPA 25 mg (n=114) or PBO + EMPA 25 mg (n=112) in study 2. LINA 5 mg significantly reduced HbA1c from baseline (randomization) vs. PBO at week 24 (primary endpoint). Changes in HbA1c were analyzed in subgroups by baseline age, HbA1c, body mass index (BMI), and renal function (estimated glomerular filtration rate [eGFR)].

At week 24, LINA 5 mg was associated with improvements in HbA1c vs. PBO as add-on to EMPA 10 mg or 25 mg and Metformin in all subgroups of patients with T2DM.

On Metformin background, LINA 5 mg as add-on to EMPA 10 mg or EMPA 25 mg improved glycemic control vs. PBO as add-on to EMPA 10 mg or EMPA 25 mg for 24 weeks irrespective of baseline age, BMI, HbA1c, and eGFR in patients with T2DM.

Table.

	EMPA 10 mg and Metformin (study 1)		EMPA 25 mg and Metformin (study 2)	
HbA1c (%)	**PBO**	**LINA 5 mg**	**PBO**	**LINA 5 mg**
Baseline age				
<65 years, n	100	98	90	86
Change from baseline at week 24, %	–0.19 (0.08)	–0.52 (0.08)	–0.11 (0.07)	–0.49 (0.08)
Difference vs. PBO at week 24		–0.32		–0.38
(95% CI)		(–0.54, –0.11)		(–0.58, –0.17)
p-value		0.0034		0.0005
65 to 75 years, n	21	20	15	22
Change from baseline at week 24, %	–0.14 (0.17)	–0.51 (0.17)	-0.04 (0.18)	-0.88 (0.15)
Difference vs. PBO at week 24		-0.36		-0.84
(95% CI)		(-0.83, 0.11)		(-1.30, -0.38)
p-value		0.1311		0.0004
Baseline BMI				
<25 kg/m^2, n	16	12	7	7
Change from baseline at week 24, %	-0.12 (0.20)	-0.91 (0.22)	0.12 (0.27)	-0.11 (0.27)
Difference vs. PBO at week 24		-0.79		-0.23
(95% CI)		(-1.37, -0.21)		(-0.98, 0.51)
p-value		0.0083		0.5396
25 to <30 kg/m^2, n	41	40	39	46
Change from baseline at week 24, %	-0.18 (0.12)	-0.45 (0.12)	-0.12 (0.11)	-0.67 (0.10)
Difference vs. PBO at week 24		-0.27		-0.55
(95% CI)		(-0.62, 0.07)		(-0.85, -0.25)
p-value		0.1166		0.0004
30 to <35 kg/m^2, n	44	43	31	35
Change from baseline at week 24, %	-0.36 (0.12)	-0.45 (0.12)	-0.10 (0.13)	-0.59 (0.12)
Difference vs. PBO at week 24		-0.09		-0.49
(95% CI)		(-0.42, 0.23)		(-0.84, -0.15)
p-value		0.5684		0.0056

	EMPA 10 mg and Metformin (study 1)		EMPA 25 mg and Metformin (study 2)	
HbA1c (%)	**PBO**	**LINA 5 mg**	**PBO**	**LINA 5 mg**
≥35 kg/m², n	24	27	31	21
Change from baseline at week 24, %	–0.03 (0.16)	–0.59 (0.15)	–0.14 (0.13)	–0.50 (0.15)
Difference vs. PBO at week 24		–0.56		–0.35
(95% CI)		(–0.99, –0.13)		(–0.75, 0.04)
p-value		0.0102		0.0769
Baseline HbA1c				
<8.5%, n	90	91	86	89
Change from baseline at week 24, %	–0.05 (0.08)	–0.39 (0.08)	–0.01 (0.07)	–0.44 (0.07)
Difference vs. PBO at week 24		–0.34		–0.43
(95% CI)		(–0.57, –0.11)		(–0.63, –0.22)
p-value		0.0036		<0.0001
≥8.5%, n	35	31	22	20
Change from baseline at week 24, %	–0.63 (0.13)	–0.97 (0.14)	–0.54 (0.16)	–1.16 (0.15)
Difference vs. PBO at week 24		–0.33		–0.62
(95% CI)		(–0.72, 0.05)		(–1.05, –0.19)
p-value		0.0875		0.0046
Baseline renal function				
eGFR ≥90 mL/min/1.73 m², n	54	66	53	46
Change from baseline at week 24, %	–0.08 (0.11)	–0.54 (0.10)	–0.10 (0.09)	–0.72 (0.10)
Difference vs. PBO at week 24		–0.47		–0.62
(95% CI)		(–0.75, –0.18)		(–0.89, –0.35)
p-value		0.0013		<0.0001
eGFR 60 to <90 mL/min/1.73 m², n	59	51	52	59
Change from baseline at week 24, %	–0.30 (0.09)	–0.50 (0.11)	–0.11 (0.10)	–0.44 (0.09)
Difference vs. PBO at week 24		–0.20		–0.34
(95% CI)		(–0.49, 0.08)		(–0.60, –0.08)
p-value		0.1588		0.0111

Changes from baseline are adjusted mean (SE) based on MMRM (including respective subgroup, treatment, baseline eGFR [where this is not the subgroup investigated], region, visit, treatment by visit interaction, visit by subgroup interaction, treatment by subgroup interaction, and treatment by visit by subgroup interaction as fixed effects, and baseline HbA1c as a linear covariate [where this is not the subgroup investigated]) in patients who received ≥1 dose of study drug during the double-blind period, and had a baseline HbA1c and ≥1 on-treatment value (observed cases, excluding values after initiation of rescue therapy). Differences vs. PBO are adjusted means. eGFR, estimated glomerular filtration rate using Modification of Diet in Renal Disease equation. This study was not powered to detect treatment differences between these baseline demographics.

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1136-P

Time Course of Change in Glycemic Parameters and Weight with Saxagliptin (SAXA) + Dapagliflozin (DAPA) Dual Add-on to Metformin (MET) Extended Release (XR) in Type 2 Diabetes (T2D)

GEOFFREY REZVANI, HUNGTA CHEN, STELLA HAN, TRACI A. MANSFIELD, *Fort Washington, PA*

A recent phase 3 trial showed that SAXA+DAPA as dual add-on to MET XR significantly reduced A1c at wk 24 vs. MET XR + SAXA or DAPA alone without increases in hypoglycemia risk or weight. This post-hoc analysis explored the time course of effect for selected outcomes.

Adults with T2D inadequately controlled with MET (≥1500 mg/d) were randomized to SAXA (5 mg/d) + DAPA (10 mg/d) + MET XR, SAXA+MET XR, or DAPA+MET XR. Adjusted mean changes from baseline were evaluated at each follow-up visit (wks 6, 12, 18 and 24) for A1c, fasting plasma glucose (FPG), and weight, and the percent of the wk 24 effect that was seen at wk 6 was calculated.

Greater reductions in A1c, FPG, and weight were observed at each time point with SAXA+DAPA+MET vs. SAXA or DAPA + MET. For each of these outcomes, a greater percentage of the wk 24 effect was achieved at wk 6 for SAXA+DAPA+MET vs. SAXA or DAPA + MET.

Adverse events were similar across treatment groups and have been published previously. eGFR with SAXA+DAPA+MET was decreased from baseline at wk 6 (LS mean change [SE] from baseline –3.1 [0.9] mL/min/1.73m²) but returned to baseline by wk 24 (LS mean change [SE] from baseline 0.8 [1.1] mL/min/1.73m²).

These results suggest that dual addition of SAXA + DAPA to MET may help patients achieve glycemic goals faster than adding either SAXA or DAPA alone in those with inadequate response to MET.

Table.

	SAXA+DAPA+MET XR n=179	SAXA+MET XR n=176	DAPA+ MET XR n=179
A1c			
Mean (SD) baseline, %	8.9 (1.2)	9.0 (1.1)	8.9 (1.2)
LS Mean (SE) change from baseline at Week 6, %	–1.1 (0.1) [a, b]	–0.6 (0.1)	–0.8 (0.1)
LS Mean (SE) change from baseline at Week 24, %	–1.5 (0.1) [a, b]	–0.9 (0.1)	–1.2 (0.1)
Ratio of week 6 to week 24 effect, % (SE) [Confidence interval]	77.8 (3.5) [70.9, 84.8]	65.0 (5.6) (54.1, 75.9)	68.9 (4.1) (60.8, 77.0)
FPG			
Mean (SD) baseline, mg/dL	181.0 (45.5)	191.6 (45.4)	185.0 (47.6)
LS Mean (SE) change from baseline at Week 6, mg/dL	–35.4 (2.7) [a]	–14.1 (2.7)	–28.2 (2.7)
LS Mean (SE) change from baseline at Week 24, mg/dL	–37.8 (2.8) [a]	–14.0 (2.9)	–31.7 (2.8)
Ratio of week 6 to week 24 effect, % (SE) [Confidence interval]	93.8 (7.8) [78.5, 109.0]	100.6 (22.2) [57.0, 144.2]	88.8 (9.2) [70.8, 106.8]
Weight			
Mean (SD) baseline, kg	87.1 (18.0)	88.0 (18.7)	86.3 (18.6)
LS Mean (SE) change from baseline at Week 6, kg	–1.3 (0.2) [a]	0 (0.2)	–1.2 (0.2)
LS Mean (E) change from baseline at Week 24, kg	–2.1 (0.2) [a]	0 (0.2)	–2.4 (0.2)
Ratio of week 6 to week 24 effect, % (SE) [Confidence interval]	65.3 (7.7) [50.2, 80.4]	NE (NE) [NE]	50.4 (6.0) [38.6, 62.2]

LS=least square; NE=not evaluable; SD=standard deviation; SE=standard error. [a]P<0.05 for the treatment comparison between SAXA+DAPA+MET XR and SAXA+MET XR. [b]P<0.05 for the treatment comparison between SAXA+DAPA+MET XR and DAPA+MET XR.

1137-P

Recovery of Postprandial Insulin Response as Mediated by Glucotoxicity Elimination with SGLT2 Inhibitor

YUTAKA MORI, SHOKO SAWANO, HIROSHI TAKAHASHI, YOSUKE NAGAI, HIROFUMI SUZUKI, KAZUNORI UTSUNOMIYA, *Tokyo, Japan*

Objective: We investigated whether improvements of hyperglycemia with SGLT2 inhibitor (SGTT2i) may also be associated with recovery of postprandial bolus insulin response.

Methods: This study included a total of 8 type 2 diabetic patients admitted for glycemic control (HbA1c, 12.5 ± 2.2%; urinary C-peptide, 66.3 ± 22.8 µg/day) who were given SGLT2i and in whom meal tolerance test (MTT) with the same diabetic meal (consisting of the same calories and nutrients) were performed at admission and after improvement of glycemic control. Of these, 6 were drug-naïve, 5 of whom received SGLT2i and intensive insulin therapy after admission, and 1 each received SGLT2i alone or combination with Metformin. They were evaluated for their glucose, insulin and C-peptide values before and 30, 60 or 120 minutes during MTT. Additionally, urinary C-peptide were also measured at admission and after improvement of glycemic control.

Results: All patients receiving intensive insulin therapy and SGLT2i, withdrew insulin therapy during their hospital stays. Their total area under the 2-hour insulin or C-peptide response curve (AUC for insulin or C-peptide) during MTT and urinary C-peptide were significantly ($p<0.01$) increased after improvement of glycemic control, compared to those at admission. The insulinogenic index varied depending on the patient. Among those on intensive insulin therapy and SGLT2i, increases were seen in AUC for insulin or C-peptide and urinary C-peptide but not in insulinogenic index. The drug-naïve patients receiving SGLT2i alone were associated with increases in insulinogenic index but decreases AUC for insulin during MTT.

Conclusions: In type 2 diabetic patients with poor glycemic control, combination therapy with insulin and SGLT2i led to early elimination of glucotoxicity and proved helpful in allowing these patients to withdrawn insulin therapy, with recovery of postprandial bolus insulin response made possible through elimination of background glucotoxicity.

For author disclosure information, see page A696.

1138-P

Inhibition Kinetics, Sidedness of Action, and Transporter-mediated Uptake of the Sodium/Glucose Cotransporter (SGLT) 2 Inhibitor Canagliflozin: Implications for Its Pharmacodynamic and Pharmacokinetic Features

RYUICHI OHGAKI, LING WEI, KAZUNORI YAMADA, TAIKI HARA, CHIAKI KURIYAMA, SUGURU OKUDA, KIICHIRO UETA, LAURENT LECLERCQ, RAO NVS MAMIDI, MASAHARU SHIOTANI, SHUSHI NAGAMORI, YOSHIKATSU KANAI, *Suita, Japan, Toda, Japan, Beerse, Belgium, Raritan, NJ*

Canagliflozin is a selective sodium/glucose cotransporter (SGLT) 2 inhibitor which suppresses the renal reabsorption of glucose and decreases blood glucose level in patients with type 2 diabetes. Canagliflozin also modestly inhibits SGLT1 in the intestine at clinical dosage. To reveal its mechanism of action, we investigated the interaction of canagliflozin with SGLT1 and SGLT2. Inhibition kinetics and transporter-mediated uptake were investigated in human SGLT1- or SGLT2-expressed cells. Canagliflozin competitively inhibited SGLT1 and SGLT2 with high potency and selectivity for SGLT2. Inhibition constant (K_i) values for SGLT1 and SGLT2 were determined to be 770.5 nmol/l and 4.0 nmol/l, respectively. ^{14}C-canagliflozin was transported by SGLT2; however, the transport rate was less than that of SGLT-specific substrate, α-methyl-d-glucopyranoside (AMG). To determine the sidedness of inhibitory effect, whole-cell patch clamp recording was performed. Canagliflozin suppressed AMG-induced SGLT1- and SGLT2-mediated inward currents preferentially from the extracellular side and not from the intracellular side. From the K_i values and the sidedness of action, canagliflozin is estimated to sufficiently inhibit SGLT2 in renal proximal tubules from the urinary side, whereas renal SGLT1 would not be inhibited, thereby contributing to the prevention of hypoglycemia. Canagliflozin most likely suppresses SGLT1 in the small intestine from the luminal side as the luminal concentration of the drug would be substantially elevated after oral administration, whereas it does not affect SGLT1 in other organs such as heart and skeletal muscle considering the maximal concentration of plasma unbound canagliflozin. After binding to SGLT2, canagliflozin would be, at least in part, reabsorbed by SGLT2, which leads to the low urinary excretion and prolonged drug action.

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1139-P

Latent Autoimmune Diabetes in an Adult Initially Thought to Have Type 2 Diabetes Mellitus, Diagnosed after Developing Diabetic Ketoacidosis Secondary to the Use of Sodium Glucose Co-transporter 2 Inhibitors

GEORGIOS K. DIMITRIADIS, RASHMI MANJUNATHA, CHRISTOPHER HARROLD, RANGANATHA RAO, HAMMAD A. BAJWA, SHUJAH DAR, NITIN GHOLAP, HARPAL S. RANDEVA, SAILESH SANKARANARAYANAN, NARASIMHA MURTHY, *Coventry, United Kingdom*

Latent Autoimmune Diabetes in Adults (LADA) is the most common term describing patients with a type 2 diabetic phenotype combined with islet antibodies and slowly progressive β-cell failure. Sodium Glucose co-Transporter 2 (SGLT2) inhibitors, act by lowering the renal threshold for glucose excretion. They suppress renal glucose reabsorption and thereby increase urinary glucose excretion. Hyperglycemia is thus ameliorated. A 57-year-old Caucasian lady presented acutely in 2010 to the emergency department with lethargy, polyuria and polydipsia and was diagnosed with type 2 diabetes mellitus (T2DM) following a blood glucose of 20.3mmol/L. Inpatient management, involved intravenous insulin to which she responded well and was later discharged on 2gr Metformin, 160mg Gliclazide and lifestyle advise. Her Body Mass Index (BMI) was 38Kg/m^2, placing her in the obese class 2 category. Following the diagnosis of T2DM, managing her overall control proved to be difficult and she repeatedly attended the emergency department with hyperglycemias. In December 2014, in view of her increasing weight and high HbA1c (126 mmol/mol) a trial with SGLT2 inhibitors was offered. In March 2015 she attended again A and E after she was found confused by her family having worsened shortness of breath over the past couple of days. She was found to have a PH of 7.01, and ketonemia (5.7 mmol/L) and the local DKA protocol was initiated. Investigations revealed positive auto-antibodies to glutamic acid decarboxylase (GAD: 614kIU/L with UNL <10kIU/L) and the diagnosis of LADA was made. She has since then been on basal bolus insulin with good response and latest HbA1c at 67mmol/mol. This case highlights the diagnostic pitfalls occuring from overlapping phenotypic characteristics between T2DM and LADA and, the importance of increased awareness in the management of such patients.

1140-P

TTP399, a Novel, Liver Selective Glucokinase Activator: Results from a 10-Day Pilot Study in Patients with Type 2 Diabetes Mellitus (T2DM) Naïve to Drug

CARMEN VALCARCE, IMOGENE DUNN, JENNIFER FREEMAN, *High Point, NC*

TTP399 is a novel, small molecule, orally available liver-selective Glucokinase Activator (GKA) in Phase 2 development. The aim of this pilot study was to examine the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of TTP399 in subjects with T2DM that were naïve to drug treatment. Sixteen subjects completed 10 days dosing of TTP399 [50, 200 or 400mg QD] or placebo in three cohorts during this multi-center, randomized, placebo-controlled, double-blind, ascending dose inpatient trial. An Ensure® Plus challenge and standardized meals were administered at baseline and Day 10 to characterize PD effects. Mean (±SD) age, HbA1c, and BMI were 56±10 years, 6.9±1%, and 32±4.6 kg/m^2, respectively.

TTP399 was safe and well-tolerated. No hypoglycemia adverse events were observed during the study. There were no changes in lactate and insulin after dosing further supporting the safety of TTP399.

All TTP399 doses administered produced measurable blood concentrations of TTP399. Cmax and AUC values increased in a dose proportional manner both on treatment Day 1 and treatment Day 10.

The observed PD effects were consistent with those expected from a liver-selective GKA. Covariance analysis of fasting plasma glucose (FPG) and post-prandial plasma glucose (AUC1-6h) levels across treatment groups, relative to placebo, showed significant reduction in FPG in the 200 and 400 mg cohorts ($p<0.005$, $p<0.05$) and glucose AUC1-6h in the 400 mg dose cohort ($p<0.05$) after 10 days of dosing. In addition to the improvement on glycemic profile, a trend towards lowering LDLc and triglycerides in the TTP399 treated subjects was noted.

The positive effects of TTP399 on regulating blood glucose in this mildly diabetic population combined with the lack of hypoglycemia support the potential safety and usefulness of liver-specific GK activators.

1141-P

Efficacy and Safety of Dapagliflozin in Patients with Type 2 Diabetes (T2D): Outcomes by Body Mass Index (BMI)

ALLA SHATSKOV, GEOFFREY REZVANI, TRACI MANSFIELD, *Fort Washington, PA*

Using data pooled from 10, 24-week placebo (PBO)-controlled studies of dapagliflozin (DAPA) as monotherapy or add-on therapy to other antidiabetes drugs in patients with T2D, we conducted a posthoc analysis assessing the efficacy and safety of DAPA 5 and 10 mg/d in subgroups by baseline BMI category. At baseline, mean age (54-60 y), T2D duration (6.0-10.2 y), and A1c (8.12%-8.33%) were similar across treatment and BMI groups. Mean fasting C-peptide values ranged from 2.1 to 4.9 ng/mL, increasing with increasing BMI. At week 24, DAPA 5 and 10 mg/d significantly reduced A1c and body weight from baseline vs. PBO across all BMI subgroups (Table). In addition, substantially more overweight (11% and 13% vs. 5%) and obese (18%-27% and 20%-29% vs. 9%-13%) patients shifted 1 BMI category lower with DAPA 5 and 10 mg/d vs. PBO, respectively. Genital (0-13.6% vs. 0.1%-1.1%) and urinary tract (2.6%-9.6% vs. 2.2%-6.4%) infections were more frequent with DAPA vs. PBO across subgroups and appeared to be more frequent with higher BMI. Hypoglycemia (excluding data after rescue) rates were similar or higher with DAPA (7.0%-16.5%) vs. PBO (8.5%-11.9%) and did not appear to differ by BMI; major hypoglycemia was reported for 4 patients (BMI 18.5-<25, DAPA 5 mg/d; 25-<30, PBO; 30-<35, DAPA 10 mg/d [n=2]). These data support DAPA as an effective and well-tolerated treatment option for patients with T2D and BMI ranging from 18.5 to ≥40 kg/m^2.

Table. End Points at Week 24.

	BMI 18.5–<25 kg/m^2			BMI 25–<30 kg/m^2			BMI 30–<35 kg/m^2			BMI 35–<40 kg/m^2			BMI ≥40 kg/m^2		
		DAPA			DAPA			DAPA			DAPA			DAPA	
	PBO (N=176)	5 mg (N=77)	10 mg (N=142)	PBO (N=632)	5 mg (N=216)	10 mg (N=672)	PBO (N=740)	5 mg (N=272)	10 mg (N=770)	PBO (N=396)	5 mg (N=136)	10 mg (N=433)	PBO (N=219)	5 mg (N=66)	10 mg (N=216)
A1C*, %															
Baseline mean (SD)	8.31 (0.98)	8.27 (1.09)	8.20 (1.10)	8.17 (1.00)	8.31 (0.95)	8.18 (0.96)	8.11 (0.91)	8.29 (0.94)	8.13 (0.90)	8.13 (0.86)	8.14 (0.93)	8.17 (0.94)	8.22 (0.90)	8.18 (0.83)	8.21 (1.01)
n at week 24	122	67	115	452	182	571	511	238	640	254	99	338	128	51	182
Adj mean change from baseline (95% CI)	−0.37 (−0.54, −0.20)	−0.63 (−0.86, −0.41)	−0.84 (−1.01, −0.66)	−0.38 (−0.45, −0.30)	−0.89 (−1.01, −0.77)	−0.80 (−0.86, −0.73)	−0.25 (−0.31, −0.18)	−0.73 (−0.84, −0.63)	−0.79 (−0.85, −0.73)	−0.27 (−0.36, −0.18)	−0.72 (−0.87, −0.57)	−0.73 (−0.81, −0.64)	−0.22 (−0.37, −0.08)	−0.95 (−1.19, −0.71)	−0.79 (−0.92, −0.65)
Adj mean diff vs PBO (95% CI)		−0.26 (−0.52, −0.01)	−0.47 (−0.67, −0.26)		−0.51 (−0.66, −0.37)	−0.42 (−0.52, −0.32)		−0.49 (−0.61, −0.36)	−0.54 (−0.63, −0.45)		−0.45 (−0.63, −0.28)	−0.46 (−0.58, −0.34)		−0.73 (−1.00, −0.46)	−0.56 (−0.75, −0.38)
Body weight†, kg															
Baseline mean (SD)	64.1 (9.0)	61.6 (9.4)	63.5 (9.0)	78.3 (9.8)	76.5 (10.5)	77.9 (10.2)	91.3 (11.0)	89.5 (11.3)	91.0 (11.7)	103.8 (12.5)	101.0 (13.0)	104.0 (12.7)	120.9 (17.3)	117.9 (15.3)	123.2 (18.7)
n at week 24	124	67	116	459	182	576	518	240	649	258	101	344	130	52	185
Adj mean change from baseline (95% CI)	0.4 (−0.0, 0.8)	−0.8 (−1.4, −0.3)	−1.0 (−1.4, −0.5)	−0.3 (−0.5, −0.0)	−1.8 (−2.2, −1.4)	−2.0 (−2.2, −1.8)	−0.7 (−0.9, −0.4)	−1.8 (−2.1, −1.4)	−2.6 (−2.8, −2.4)	−0.6 (−1.0, −0.2)	−1.9 (−2.5, −1.2)	−2.8 (−3.2, −2.5)	−0.8 (−1.5, −0.1)	−2.4 (−3.6, −1.2)	−3.4 (−4.0, −2.7)
Adj mean diff vs PBO (95% CI)		−1.2 (−1.9, −0.6)	−1.3 (−1.9, −0.8)		−1.6 (−2.0, −1.1)	−1.7 (−2.0, −1.4)		−1.1 (−1.6, −0.7)	−2.0 (−2.3, −1.6)		−1.3 (−2.0, −0.5)	−2.2 (−2.7, −1.8)		−1.6 (−3.0, −0.2)	−2.6 (−3.5, −1.6)

*P=0.0029; †P<0.0001 for treatment by BMI subgroup interaction. Results are excluding data after rescue, including patients with nonmissing values, and analyzed using longitudinal repeated measures analysis. Data were pooled from the following studies: NCT00528372, NCT00528879, NCT00683878, NCT00680745, NCT00673231, NCT00984867, NCT00855166, NCT01031680, NCT01042977, and NCT00859898. Adj=adjusted; Diff=difference.

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1142-P

The Clinical Efficacy and Treatment Satisfaction of Weekly DPP-4 Inhibitors in Japanese Patients with Type 2 Diabetes Mellitus

TAKAHIRO TOSAKI, HIDEKI KAMIYA, TATSUHITO HIMENO, YOSHIRO KATO, MASAKI KONDO, AKEMI INAGAKI, YUKA YAMAMOTO, RYUICHI MIZUBAYASHI, KAORI TSUBONAKA, CHIE OSHIRO, YUKI NAKAYA, JIRO NAKAMURA, *Nagoya, Japan, Nagakute, Japan, Yokkaichi, Japan*

DPP-4 inhibitors (DPP-4i) play an important role in treating patients with type 2 diabetes mellitus in Japan. Weekly DPP-4i have recently become available with their usefulness anticipated. We have investigated the clinical efficacy and Treatment Satisfaction of weekly DPP-4i, trelagliptin or omarigliptin, in 44 out-patients with type 2 diabetes mellitus. 20 patients previously treated with other DPP-4i were switched to weekly DPP-4i with the rest of antidiabetics unchanged. 24 patients naive to DPP-4i were treated with weekly DPP-4i as add-on to previous treatment. Random capillary blood glucose (RCBG) test, HbA1c, glycoalbumin (GA), body weight, and Diabetes Treatment Satisfaction Questionnaire (DTSQs) were evaluated. Patients who have been switched from other DPP-4i had no significant change in HbA1c and GA at 3 months. HbA1c and GA of patients who had been naive to DPP-4i significantly improved from 9.29 ± 2.38% to 6.76 ± 0.85% ($p<0.001$) and 26.2 ± 11.8% to 16.3 ± 3.6% ($p<0.005$) respectively. Nausea and diarrhea were observed as side effects in 2 cases. In DTSQs, total score of the first factor consisted of the six treatment satisfaction items significantly improved from 25.3 ± 7.8 to 30.3 ± 4.7 ($p<0.05$) in patients switched to weekly DPP-4i and from 20.3 ± 8.5 to 28.1 ± 5.7 ($p<0.001$) in patients who had been naive to DPP-4i. Scores of 6 items including overall satisfaction, convenience, flexibility, level of understanding, recommendation, and satisfaction to continue treatment significantly improved in patients who had been naive to DPP-4i and the trend was similar and significant in 39 patients who were taking other daily medication. Weekly DPP-4i are effective and well-tolerated treatment which improves patients' treatment satisfaction.

1143-P

Impact of SGLT2 Inhibitor Tofogliflozin on Hyperinsulinemia and Fatty Liver (FL) through Hepatic Insulin Clearance (HIC) in Patients with Type 2 Diabetes Mellitus (T2DM)

YASUHIRO MATSUBAYASHI, HIDEKI SUGANAMI, KOHEI KAKU, HIROHITO SONE, *Niigata, Japan, Tokyo, Japan, Okayama City, Japan*

Chronic hyperinsulinemia has been associated with cardiovascular disease and is frequently observed in T2DM and FL. Decreased HIC is a main cause of chronic hyperinsulinemia as well as insulin resistance and compensatory insulin hypersecretion. SGLT2 treatment significantly lowered both fasting glucose levels and fasting insulin levels (F-IRI). Although SGLT2 treatment would be expected to improve hepatic insulin sensitivity, a number of points are unclear for HIC changes with SGLT2 therapy. This study evaluated the impact of tofogliflozin (TOFO) on HIC focusing on the presence or absence of FL in patients with T2DM. Analyzed were 363 drug-naïve Japanese T2DM patients on diet and exercise therapy who received TOFO as initial monotherapy in 2 TOFO phase 3 studies. HIC was calculated by fasting C-peptide (pmol/l)/insulin (pmol/l). Patients were divided into 2 groups based on the presence or absence of FL using the fatty liver index. Changes in variables from baseline to week 24 were analyzed by the Wilcoxon signed rank test or analysis of covariance model with each group as a fixed effect and baseline variables as covariates. Baseline characteristics differed significantly between FL(+) vs. FL(-) for age [56 vs. 61 y, $p<0.001$], BMI (27.6 vs. 21.9 kg/m2, $p<0.001$), F-IRI (68.9 vs. 30.3 pmol/l, $p<0.001$), and HIC (9.5 vs. 12.5, $p<0.001$), but not HbA1c. At week 24, with TOFO there were significant ($p<0.001$) reductions in HbA1c (-0.79 vs. -0.68%), body weight (-3.0 vs. -2.6 kg), and F-IRI (-17.4 vs. -8.1 pmol/l) and increases in HIC (22.2 vs. 24.4%). Aspartate aminotransferase-to-platelet ratio index (APRI), a noninvasive marker of liver fibrosis, and liver enzymes were reduced significantly in the FL(+) group compared with FL(-). Results indicated that TOFO could improve hyperinsulinemia and increase HIC levels in both FL(+) and FL(-) patients. In addition, TOHO improved liver fibrosis markers in FL(+).

1144-P

Effects of Leucine-Metformin Combinations on Glycemic Control in Type 2 Diabetes

KEVIN NISWENDER, ORVILLE KOLTERMAN, MARY KOSINSKI, MICHAEL B. ZEMEL, *Nashville, TN, San Diego, CA, Knoxville, TN*

We previously showed leucine (Leu) to activate Sirt1 signaling and amplify the effects of Metformin (Met), resulting in Leu-Met synergy in preclinical studies. We have now conducted a phase 2A study to test the efficacy of Leu-Met combinations vs. standard Met in patients with type 2 diabetes. Following a 4 week washout from monotherapy, 96 patients were randomized into 4 study arms: 2.2 g Leu/250 mg Met/day, 2.2 g Leu/500 mg Met, 2.2 g Leu/1000 mg Met or 1700 mg Met (active control) for 28 days. All treatments were well tolerated with similar adverse events reported. Meal tolerance tests (MTT) were conducted at treatment days 0 and 28 to assess total and incremental area under the glucose curve (AUC). Additional outcomes included fasting plasma glucose and insulin, HbA1c and 24-hour glucose via continuous glucose monitoring (CGM). The mid- and high doses of Leu-Met dose-responsively improved all measures of glycemic control, while the lowest dose did not. The Met control arm exhibited greater improvements in fasting glucose ($p<0.05$), average daily glucose ($p<0.05$) and total, but not incremental, glucose AUC (p=NS) in the per protocol cohort, while the intention-to-treat (ITT) cohort showed comparable glucose improvements between Leu-Met and Met control. Notably, the Met control arm exhibited markedly greater improvements in glucose and glucodynamics than expected from previous reports. The Met control arm had an ~twofold greater loss of glycemic control during washout ($p<0.05$) resulting in poorer baseline control and a larger potential improvement with treatment compared to the other arms. Adjusting for this difference resulted in comparable effects of Leu-Met and Met control. Further, a responder analysis of fasting glucose and CGM showed equivalence in both responder fraction (65%) and magnitude of effect between the 2.2g Leu/1000 mg Met arm and the 1700 mg Met control arm. These data suggest that leucine can augment the effectiveness of Met to enable a significant (~40%) Met dose reduction in man.

1145-P

Absence of Direct Effect of the Sodium-Glucose Co-Transporter Inhibitors on Vascular Reactivity in Nondiabetic and Diabetic Rodents

CAROLINE DUBROCA, CLAIRE PILETTE, THIERRY SULPICE, ERIC W. MAYOUX, *Toulouse, France, Biberach, Germany*

Sodium-Glucose co-Transporter 2 (SGLT2) inhibitors emerged as a promising new treatment for type 2 diabetes. Beyond glycemic control via glucose excretion in urine, these agents also reduce blood pressure (BP) and body weight. The reduction in BP was initially thought to be mediated by the osmotic diuresis induced by these drugs. However the antihypertensive effect was still observed in patients with chronic kidney diseases while diuretic effect was dampened. Therefore, the mechanism of BP lowering effect of these agents is still not fully understood. This study aims to investigate a putative direct effect of SGLT1/2 inhibitors on vascular reactivity. The thoracic aorta, of diabetic db/db or control mice and of Sprague Dawley rats have been excised and placed in organ bath for measurement of isometric force. For rat, vascular reactivity of pulmonary artery has been also investigated. Contractile response to Phenylephrine (Phe) but also relaxation responses to Acetylcholine (endothelium-dependent) and to sodium nitropruside (endothelium-independent) have been investigated in presence or not of 500nM of empagliflozin, a specific SGLT2 inhibitor, or LX4211, a dual SGLT1/2 inhibitor. For vascular beds of rats, another SGLT2 inhibitor, Canagliflozin was also used. Empagliflozin as well as LX4211 did not exhibit direct effects on contraction or relaxation properties of aorta neither from diabetic and nondiabetic mice. In rats, none of the compounds, including canagliflozin modified the contractile responsiveness to Phe or the relaxation capabilities of Acetylcholine and sodium nitroprusside. In conclusion, despite controversial results about the presence or not of SGLT1 and SGLT2 transporters in vessels walls, our results clearly demonstrate the lack of direct effect of specific SGLT2 inhibitors as well as dual inhibitor SGLT1/2 inhibitor on vascular reactivity ruling out a putative direct effect of those new drugs to lower blood pressure.

1146-P

Polypharmacological Modulation of PPARγ/α Gene Programs Is Anabolic for Bone

BEATA LECKA-CZERNIK, *Toledo, OH*

Antidiabetic therapies are aimed at distinct mechanisms controlling glucose utilization and disposal. Glitazones, which target PPARγ insulin-sensitizing activity at the cellular level, have been proven to be robust treatments for type 2 diabetes. Unfortunately, glitazones cause adverse effects including bone loss which additionally increase fracture risk in diabetic patients who have impaired bone turnover. Recently, it has been shown that antagonists and inverse agonists of PPARγ afford insulin sensitization efficacy in animal models with improved therapeutic index; however, their effects on bone following chronic administration were previously unknown. Here, we demonstrate that SR10171 compound, an inverse PPARγ agonist and modest PPARα agonist, normalizes energy metabolism and increases bone mass by modulating osteocytes, osteoblasts, and osteoclasts activities. Treatment of DIO mice with SR10171 at the dose which normalizes glucose tolerance, results in increased trabecular and cortical bone mass due to increased bone formation and bone turnover. In vitro, SR10171 is neutral for direct effect on osteoblast

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Moderated Poster Discussion ADA-Supported Research

(OB) differentiation; however OB isolated from endosteal surface of femora of treated mice have increased expression of OB-specific gene markers. OB activation is regulated by osteocytes (OT). We have showed that SR10171 targets PPARγ/α in OT which decreases SOST and DKK1 expression - negative paracrine regulators of OB activity. At the same time, SR10171 promotes osteoclast (OC) differentiation, which accounts for increased bone turnover; however the balance is shifted toward bone formation. Moreover, SR10171 has sustained anabolic effect on bone in normoglycemic mice demonstrating the therapeutic potential of pharmacological PPARγ/α modulation in promoting the anabolic effect on bone and simultaneous improvement in insulin sensitivity.

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1147-P

Type 2 Diabetes Patients on Metformin and Well-Controlled Basal: Can Supplementary Vildagliptin Control Residual Prandial Hyperglycemia?

SYLVIA FRANC, AHMED DAOUDI, ILHAM XHAARD, CAROLINE RANDAZZO, GUILLAUME CHARPENTIER, *Corbeil-Essonnes, France, Evry, France*

In patients with type 2 diabetes (T2D) treated with Metformin and well-titrated basal insulin whose HbA1c remains above 7%, failure to optimize glycemic control is mainly due to a persistent elevation in postprandial glycaemia (PPG). Can supplementary vildagliptin reduce HbA1c to target levels (<7.0%) vs. placebo? 31 DT2 patients randomized (4F/27H) and 3 drop out, receiving Metformin at the maximum tolerated dose together with well-titrated insulin glargine (fasting blood glucose: <1.20 g/l), but with HbA1c persistently between 7 and 9%, were randomised to double-blind cross-over treatment with either vildagliptin (50mg b.i.d.) or placebo, with the 3-month treatment periods being separated by a 3-month wash-out period. Immediately prior to the end of these two periods, patients wore a continuous-glucose-monitoring device for 5 days. The amount of carbohydrates was collected at the same time for each of the 5-day meals. Baseline data were as follows: HbA1c: 7.65.±0.5%; diabetes duration 6.1±7.9 years; age: 59.4±7.6 years; BMI: 28.6±4.3; insulin glargine dose: 39.3±36.8 u/d; Metformin dose: 2.8±0.29 g/d. The proportion of patients bringing their HbA1c <7% with vildagliptin was 4 times as high as that of patients treated with placebo (28.6% vs. 7.4%, p=0.007). Furthermore, the HbA1c mean were reduced at 1% in the vildagliptin group vs. placebo (vildagliptin: -0.7 (±0.9)%; placebo= +0.3 (± 0.9)%; p= 0.002). Glucose excursions on CGM curves at mealtime, estimated through AUCs, were significantly lower with vildagliptin vs. placebo. Significantly more time was spent in the range [70-180 mg/dl] with vildagliptin vs. placebo [74.8 (±18.0)% vs. 61.1 (±22.9)%]. Conversely the time spent above 180 mg/dl was significantly lower for vildagliptin vs. placebo (21.2 (±17.9)) vs. 37.4 (±23.2). Predictors for patient response to treatment were also studied.

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1148-P

Minority Inclusion in 2014 FDA-Approved Type 2 Diabetic Drugs

CHRISTINE MERENDA, KATHRYN MARWITZ, *Silver Spring, MD, Des Moines, IA*

Approximately 29.1 million Americans, or 1 in 11 people, have diabetes in the United States. The disease burden is disproportionate though, with Native Americans having the highest rates followed by African Americans and Latinos. In 2014 the U.S. Food and Drug Administration (FDA) approved 4 new drugs to treat type 2 diabetes (T2DM); Dapagliflozin (Farxiga®), Empagliflozin (Jardiance®), Albiglutide (Tanzeum®), and Dulaglutide (Trulicity®). Three of the four products had limited testing in U.S. trial participants and even less testing in minorities.

FDA Medical Reviews, Drug Trials Snapshots, and Patient Package Inserts available on the FDA website were utilized for the current assessment. The pivotal trial for each product was assessed for inclusion, as well as subgroup analyses for safety and efficacy. Prevalence data were obtained from the Centers for Disease Control and Prevention.

Dapagliflozin and Empagliflozin are both SGLT2 inhibitors and oral agents. The pivotal trial for Dapagliflozin had 29.3% participation from North America and only 3.6% of participants were black/African American. In the case of Empagliflozin, 21.4% of pivotal trial participants were from North America. Native Americans made up 0.4% of participants and blacks/African Americans made up 3.7%. Albiglutide and Dulaglutide are both GLP-1 agonists administered once weekly as an injection. The demographic data for Dulaglutide is not ideally recorded; while the pivotal trial had a majority of participants from North American (55.7%), the sponsor reported race as white or non-white only. The non-white participants comprised 31.8%. The pivotal trial for approval of Albiglutide was a bright spot for inclusion. American Indians comprised 6.2% of participants, blacks/African Americans were 14.6% of participants, and 26.1% were Hispanic/Latino. Limited testing in minorities meant safety and efficacy analysis were also limited or even impossible. Healthcare providers are challenged to know the best treatment for minority patients.

1149-P

Alogliptin in Triple Therapy with Metformin and Sulfonylureas Provides Significant Reductions in HbA1c and Is Well Tolerated: An Analysis from the EXAMINE Trial

SIMON R. HELLER, CHRISTOPHER P. CANNON, HEENA HOWITT, KAMLESH KHUNTI, RICHARD M. BERGENSTAL, WILLIAM B. WHITE, THE EXAMINE INVESTIGATORS, *Sheffield, United Kingdom, Boston, MA, Wooburn Green, United Kingdom, Leicester, United Kingdom, Minneapolis, MN, Farmington, CT*

Patients with type 2 diabetes (T2D) often require multiple therapies to achieve glycaemic control. There has been no study evaluating alogliptin (ALO) when added to Metformin (MET) and a sulfonylurea (SU). We performed a *post hoc* analysis of the EXAMINE trial to evaluate the anti-hyperglycaemic efficacy and safety of the addition of ALO to T2D patients on existing MET and SU in this study. A substantial population in EXAMINE entered on dual therapy with MET and SU (N=1,398; ALO=693, placebo (PBO) =705) and were followed for up to 40 months (median 18 months). Investigators were allowed to change therapies according to local standard of care including the existing dose of MET and SU. The type/dose of MET and of SU were neither standardised nor controlled. In this subgroup 550 ALO and 505 PBO patients persisted to study end without addition of other anti-hyperglycaemic therapy. For all patients on MET+SU at baseline characteristics were similar for ALO and PBO groups (mean HbA1c, 8.14%). Changes from baseline for HbA1c observed in these subgroup analyses were as follows: (1) all patients randomised on baseline MET+SU: -0.38% ALO vs. +0.14% PBO, LS mean difference for change from baseline of HbA1c at last visit -0.52% (p<0.001); (2) patients persisting on MET+SU without addition of other glycaemic therapies: -0.43% ALO vs. +0.15%, LS mean difference -0.56% (p<0.001), and for the overall EXAMINE study population (–0.33% ALO vs. 0.03% PBO, LS mean difference -0.36% p < 0.001). The ALO and PBO groups did not differ in the percentage of patients with ≥ 1 adverse event (AE) (75.2% ALO and 79.6% PBO) or serious AEs (28.3% ALO and 32.1% PBO). There was no significant difference in the incidence of any report of hypoglycaemia (8.8% ALO and 6.7% PBO, p=0.161) or serious hypoglycaemia (1.30% ALO and 0.43% PBO, p=0.088). These data demonstrate that triple therapy with MET, SU and ALO in this double blind trial was effective and well tolerated.

Supported By: Takeda Pharmaceuticals International, Inc.

1150-P

Ipragliflozin, a Novel SGLT2 Inhibitor, Improves Blood Glucose, as Shown by Continuous Glucose Monitoring, and Ameliorates Metabolic Syndrome in Japanese Patients with Type 2 Diabetes Mellitus

SONEI SHOJIMA, TATSUAKI NAKATOU, *Okayama City, Japan*

Background and Aims: Ipragliflozin (Suglat®) was the first selective SGLT2 inhibitor in Japan and has become widely used since April 2014.

Aims: To assess the plasma glucose changing and efficacy and safety of Ipragliflozin.

Methods: T2DM patients with poor blood glucose control received 50 mg Ipragliflozin once daily as monotherapy or as additional therapy. Efficacy and safety were evaluated for 24 weeks. CGM was performed for one-week periods at week 0 and week 4.

Results: 14 patients were enrolled (male/female: 8/6; age: 53.6 ± 3.0 y; body weight: 79.6 ± 3.8 kg; BMI: 29.8 ± 1.0; HbA1c: 8.0 ± 0.4). CGM: The daily blood glucose curve at week 4 was consistently lower than baseline. The average whole-day blood glucose was decreased significantly, and nocturnal blood glucose, FPG, PPG, postprandial AUC 0-3h also tended to decrease. However, indicators of fluctuation, such as MAGE and standard deviation, were not changed significantly. PD: The 24-h urinary glucose excretion and urinary volume were significantly increased consistently around 90 g/day and 900 ml/day respectively. Efficacy: The change in HbA1c was -0.8% (P < 0.01) from week 4 and continued until week 24. The change in body weight was -2 to -3 kg from week 4 (P < 0.01). Waist circumference, blood pressure, HDL, and urinary urea were significantly improved. Safety: No serious adverse events (AEs), symptomatic hypoglycemia or dehydration occurred during the study. Mild AEs based on PD, such as pollakiuria, polyuria, and hunger, occurred more frequently in most patients.

Conclusion: Daily administration of Ipragliflozin was effective in improving glycemic control, body weight, and metabolic syndrome in Japanese obese T2DM patients with good safety and tolerability. We conclude that Ipragliflozin can be beneficial as monotherapy or in combination with other anti-hyperglycemic regimens in the treatment of T2DM patients.

1151-P

Efficacy and Safety of Vildagliptin, Sitagliptin, and Linagliptin as Add-on Therapy in Chinese Patients with T2DM Inadequately Controlled with Dual Combination of Insulin and Traditional Oral Hypoglycemic Agent

CHANG-LIN NI, YUN-ZHAO TANG, GANG WANG, ZHEN-HUAN JIANG, TIAN-TIAN YAN, MIN YANG, YI-JUN CHEN, LING-LING MENG, YAN-JUAN ZHU, CHEN-GUANG LI, ZHU LI, PING YU, *Tianjin, China*

We aimed to evaluate the efficacy and safety of the three dipeptidyl peptidase 4 (DPP-4) inhibitors (vildagliptin, sitagliptin, and linagliptin) as add-on therapy in Chinese patients with type 2 diabetes mellitus inadequately controlled on dual combination of insulin and Metformin or acarbose. A total of 535 T2DM patients who failed to achieve glycemic control with insulin and a traditional oral hypoglycemic agent were randomized to receive vildagliptin, sitagliptin, or linagliptin. Body mass index, glycosylated hemoglobin (HbA1c), fasting and postprandial plasma glucose (FPG and PPG), insulin dose, and adverse events were evaluated during the study. The baseline HbA1c was 9.59 ± 1.84% (vildagliptin), 9.22 ± 1.60% (sitagliptin), and 9.58 ± 1.80% (linagliptin). At week 12 the changes in HbA1c from baseline were –1.33 ± 0.11% (vildagliptin), –0.84 ± 0.08% (sitagliptin) and –0.81 ± 0.08% (linagliptin), the vildagliptin group had the greatest HbA1c reduction ($P < 0.05$). The proportions of patients that reached target HbA1c were 66.27% (vildagliptin), 52.73% (sitagliptin), and 55.49% (linagliptin), the vildagliptin group had the highest one ($P < 0.05$). The baseline FPG and PPG in the three groups were at the same level. At week 12, mean FPG in the vildagliptin (7.31 ± 1.50 mmol/L) and linagliptin (6.90 ± 1.55 mmol/L) groups were significantly lower than in the sitagliptin group (8.02 ± 4.48 mmol/L; $P < 0.05$); the linagliptin group had the lowest mean PPG ($P<0.05$). The required insulin dosage in the vildagliptin group was the lowest at weeks 6 and 12. Only mild AEs were reported. The three DPP-4 inhibitors appear to be effective and safe as add-on therapy for T2DM patients on dual combination of insulin and a traditional OHA. Vildagliptin was more effective in decreasing insulin requirement and achieving glycemic control when compared to the other two.

1152-P

SGLT2 Inhibitor Is More Effective in Type 2 Diabetes with High Threshold Glucose Concentration for Renal Glucose Excretion

TAKAYUKI WATANABE, TOMOHITO HAYASHI, KEITARO MIYAMURA, TSUYOSHI KAKEI, TATSUYA SAWAGUCHI, KAZUKI OTA, *Yokohama, Japan*

The threshold for renal glucose excretion (TRGE) was reported to be higher in diabetics than in normal controls through the increase of SGLT2 expression in the renal proximal tubules. If the TRGE of diabetics is different from patients to patients, then the increase of TRGE is one of the cause of worsening of blood glucose control in diabetics. We investigated the correlation between the effect of SGLT2 inhibitor and the TRGE in patients with T2DM. Because it is difficult to measure the precise TRGE in each patient, we defined the TRGE as the highest plasma glucose during observation with negative simultaneously measured urinary glucose. Subjects were 25 patients with type 2 diabetes mellitus (male/female = 15/10) in our outpatient office. Eighteen patients took ipragliflozin, 6 took dapagliflozin and one took tofogliflozin. Eighteen patients took Metformin, 11 took DPP-4 inhibitor, 11 took sulfonyl urea and 4 injected insulin. Mean age was 57.3 ± 12.0 years. Mean baseline hemoglobin A1c (HbA1c) was 8.7 ± 1.0%. Mean baseline BMI was 31.4 ± 5.0 kg/m^2. Mean TRGE was 195 ± 20 mg/dl. HbA1c decreased after the treatment with SGLT2 inhibitor (7.9 ± 1.1% at 12 weeks and 8.0 ± 0.9% at 24 weeks). Body weight also decreased at 12 weeks (- 2.5 ± 2.5 kg). TRGE was significantly correlated with change in HbA1c from baseline at 12 weeks ($R = 0.561$, $p = 0.0035$). TRGE was also significantly correlated with the change at 24 weeks ($N = 18$ and $R = 0.487$, $p = 0.0403$). But it was not correlated with change in body weight from baseline at 12 weeks ($R = 0.134$, NS). Baseline HbA1c may be associated with the change in HbA1c but multiple regression analysis showed that TRGE was only significant factor for the change in HbA1c. We conclude that SGLT2 inhibitor is more effective in T2DM with high threshold glucose concentration for renal glucose excretion.

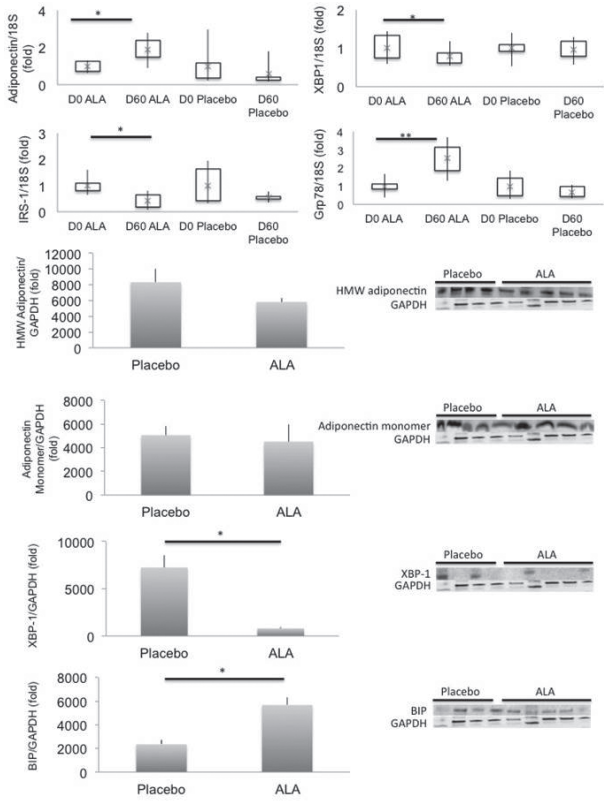
1153-P

Supplementation of Alpha-linolenic Acid Improves Endoplasmic Reticulum Stress and Adiponectin in Patients with Type 2 Diabetes

WALLACE R. HOLLANDA-MIRANDA, PATRICIA M. GOMES, REBECA A. BERALDO, MILTON C. FOSS, MARIA CRISTINA FOSS-FREITAS, *Ribeirao Preto, Brazil*

Many studies showed the anti-inflammatory effect of n-3 polyunsaturated fatty acid (PUFA). T2DM is associated with reduced of adiponectin (ADQ) and activation of endoplasmic reticulum stress (ERS), signals of chronic inflammation. We evaluated the effect of alpha-linolenic acid (n-3 ALA/a type of PUFA) supplementation in T2DM patients on the molecular expression of ADQ and ERS genes in subcutaneous abdominal adipose tissue (SAT). We performed a double-blinded placebo-controlled study with 20 T2DM patients, randomly 3g/day of ALA or placebo for 60d. SAT (collected by fine-needle aspiration) were performed before and after the supplementation. The molecular expression of ADQ and ERS genes was evaluated by real-time PCR and Western blotting (WB). The genic expression of ADQ was increased after ALA almost 90%, however we did not observe change of protein concentration (PC) by WB. In the ERS, we observed reduction of the genic expression in XBP1 (20%) and sXBP1 (70%), increase in GRP78 (150%), confirmed in PC in the SAT. Furthermore, reduction in genic expression in IL-6 (80%) and IRS-1 (6%), but it did not observed in PC. ALA may modulate ERS by the pathway of IRE1/XBP leading to increase the chaperones (BIP/GRP78), beside may modulate ADQ genic expression, but without change in PC in SAT. Improvement with n-3 ALA suggests a potential clinical utility for this agent in T2DM.

Figure.



Supported By: Coordination for the Improvement of Higher Education Personnel; São Paulo Research Foundation

1154-P

The Phosphate-Binding Resin Sevelamer Reduces Plasma Glucose Levels in Patients with Type 2 Diabetes

ANDREAS BRØNDEN, MORTEN HANSEN, KRISTIAN H. MIKKELSEN, ULRICH ROHDE, CHRISTOFFER VAABEN, DAVID P. SONNE, JENS J. HOLST, TINA VILSBØLL, FILIP K. KNOP, *Copenhagen, Denmark*

Accumulating evidence suggests that bile acids contribute to the regulation of glucose homeostasis. We examined the potential glucose-lowering action of the bile acid-sequestrating drug sevelamer carbonate (Renvela) approved for use in Europe as a phosphate binder in patients with chronic kidney disease (CKD) receiving dialysis and in CKD patients with serum phosphorous > 1.78 mmol/L. Thirty patients with type 2 diabetes and no CKD

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

were randomized to treatment with sevelamer (N=20) or placebo (N=10). Standardized 4-hour liquid meal tests with measurements of plasma glucose and serum insulin were performed following the first dose and again after 6 days of treatment (1,600 mg TID). Gastric emptying (GE) and resting energy expenditure (REE) were evaluated by the acetaminophen absorption method and indirect calorimetry, respectively. Six days of treatment with sevelamer reduced fasting plasma glucose from 8.5 to 7.7 mmol/L (P<0.001). Postprandial glucose excursions (total AUC) were significantly (P<0.001) reduced by sevelamer and a non-significant (P=0.094) decrease in baseline-subtracted glucose excursions (incremental AUC) was observed. When comparing glucose excursions between groups, sevelamer reduced incremental AUC (P=0.004) compared to placebo. Non-statistically significant increases in serum insulin were detected in subjects treated with sevelamer. Fasting levels of total and LDL cholesterol were reduced from 4.6 to 4.2 mmol/L (P=0.011) and 2.6 to 1.8 mmol/L (P<0.001), respectively, whereas triglycerides increased from 2.1 to 2.9 mmol/L (P=0.049) in the sevelamer-treated group. No changes in GE or REE were observed within or between the two groups. In conclusion, a 6-day treatment course with the phosphate-binding resin sevelamer was demonstrated to reduce fasting plasma glucose and postprandial glucose excursions in patients with type 2 diabetes. The mechanisms behind these effects remain to be established.

Supported By: Sanofi; Danish Diabetes Academy

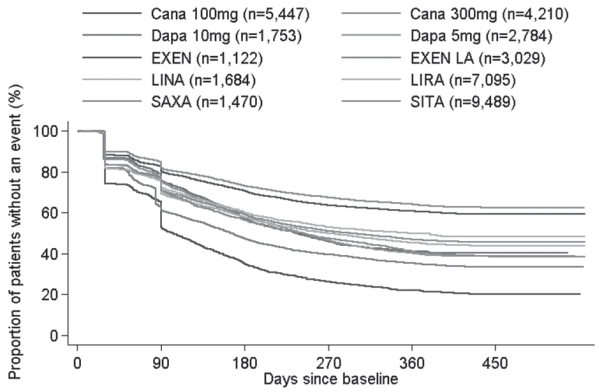
1155-P

Comparative Persistence with Antihyperglycemic Agents Used to Treat Type 2 Diabetes Mellitus in the Real World

JENNIFER CAI, YUEXI WANG, ONUR BASER, LIN XIE, JORIS DIELS, CHERYL NESLUSAN, WING CHOW, *Titusville, NJ, Ann Arbor, MI, New York, NY, Beerse, Belgium, Raritan, NJ*

Persistence with AHA therapy is an important determinant of treatment effectiveness in the real-world. This analysis aimed to compare persistence in patients receiving newer AHAs: the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin (CANA, 100 or 300 mg) and dapagliflozin (DAPA, 5 or 10 mg), vs. the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists. Patients with T2DM who received the first claim (index date) for the listed AHAs from February 2014 to October 2014 in the Truven Health Analytics MarketScan® database (commercial) were included. Continuous enrollment for 6 months pre- and 9 months post index was required. Time to discontinuation and proportion of patients remaining on treatment were presented by Kaplan-Meier curves. Of the 38,083 patients identified, mean (SD) age was 52 (8) years and the Charlson Comorbidity Index (a measure of health status) was 2.4 (1.6). Nearly 67% of patients on CANA remained on treatment after 9 months compared with approximately half or less for the DAPA (46%), DPP-4 inhibitors (47% to 53%), and GLP-1 receptor agonists (26% to 50%) cohorts (Figure 1). In this analysis, a higher proportion of CANA patients appear to have continued with treatment longer vs. the other newer AHAs studied. As such, CANA may have better effectiveness and/or tolerability in actual clinical practice.

Figure 1. Kaplan-Meier Curves Showing Time to Discontinuation.*



* Discontinuation was defined as an observed refill gap of ≥90 days between 2 subsequent prescriptions.
** SGLT2 inhibitors: canagliflozin (CANA) 100 mg and 300 mg, dapagliflozin (DAPA) 5 mg and 10 mg
DPP-4 inhibitors: sitagliptin (SITA), saxagliptin (SAXA), linagliptin (LINA)
GLP-1 receptor agonists: liraglutide (LIRA), exenatide (EXEN), exenatide long-acting (EXEN LA)

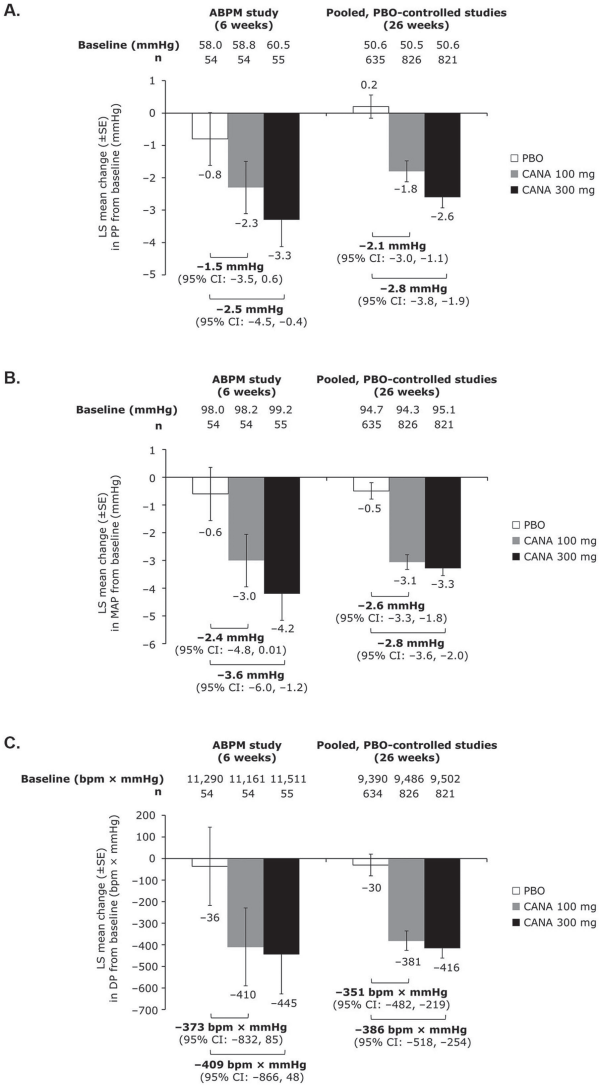
1156-P

Blood Pressure (BP) Effects of Canagliflozin (CANA) in Patients with Type 2 Diabetes Mellitus (T2DM)

MICHAEL PFEIFER, RAYMOND TOWNSEND, MICHAEL J. DAVIES, UJJWALA VIJAPURKAR, JIMMY REN, *Raritan, NJ, Philadelphia, PA*

T2DM is associated with increased cardiovascular (CV) morbidity and mortality. Physiologic determinants such as pulse pressure (PP = difference between systolic BP [SBP] and diastolic BP [DBP)], mean arterial pressure (MAP = 2/3 DBP + 1/3 SBP), and double product (DP = heart rate × SBP) are linked to CV outcomes. The effects of CANA on PP, MAP, and DP were assessed using sitting BP assessments based on pooled 26-week data from 4 studies of CANA 100 and 300 mg vs. placebo (PBO) in patients with T2DM (N = 2313; mean age, 56 y; A1c, 8.0%; BMI, 32 kg/m^2; SBP, 128 mmHg) and the 6-week ambulatory BP monitoring (ABPM) study in patients with T2DM and hypertension (N = 169, mean age, 59 y; A1c, 8.1%; BMI, 33 kg/m^2; SBP, 139 mmHg) using the averaged 24-hour BP assessments. In the pooled studies, CANA 100 and 300 mg provided reductions in SBP (-4.3 and -5.0 vs. -0.3 mmHg) and DBP (-2.5 and -2.4 vs. -0.6 mmHg) vs. PBO at week 26. Reductions in PP, MAP, and DP were also seen with CANA 100 and 300 mg vs. PBO (Figure). In the ABPM study, CANA 100 and 300 mg provided reductions in mean 24-hour SBP (-4.5 and -6.2 vs. -1.2 mmHg) and DBP (-2.2 and -3.2 vs. -0.3 mmHg) vs. PBO at week 6. Relative to PBO, CANA 300 mg provided reductions in PP and MAP; CANA 100 mg had more modest effects on these parameters. In summary, CANA improved all 3 CV physiologic markers, consistent with the hypothesis that CANA may have beneficial effects on some CV outcomes in patients with T2DM.

Figure. Change from Baseline in (A) PP, (B) MAP, and (C) DP with CANA vs. PBO.



SE, standard error; bpm, beats per minute.

Supported By: Janssen Scientific Affairs, LLC

1157-P

Hormonal Responses during Hypoglycemia with Dipeptidyl Peptidase-4 Inhibitor Linagliptin and Glucagon-like Peptide-1 Receptor Agonist Liraglutide in Patients with Type 2 Diabetes

DAISUKE YABE, TAKASHI ETO, MASANARI SHIRAMOTO, SHIN IRIE, KENTA MUROTANI, YUSUKE SEINO, HITOSHI KUWATA, TAKESHI KUROSE, SUSUMU SEINO, BO AHRÉN, YUTAKA SEINO, *Kobe, Japan, Fukuoka, Japan, Nagakute, Japan, Nagoya, Japan, Lund, Sweden*

Dipeptidyl peptidase-4 inhibitors (DPP-4i) enhance actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) on secretions of insulin and glucagon to control glycaemia. While DPP-4i add-on to insulin therapies reduces the risk for hypoglycemia, possibly through augmentation of GIP actions on glucagon secretion, this model needs to be tested. The objective of this study was therefore to determine the effects of DPP-4i linagliptin on glucagon and other counter-hormone responses to hypoglycemia, and to compare these to those of the GLP-1 receptor agonist (GLP-1RA) liraglutide. Japanese type 2 diabetes patients who were either drug-naïve or treated with a single oral hypoglycemic agent were randomly assigned to DPP-4i linagliptin or GLP-1RA liraglutide and received either one of the drugs once daily for 14 days, thereafter meal test and a three-step hypoglycemic clamp tests (7.5, 5.0 and 2.5 mM glucose) were undertaken. The changes of plasma glucagon levels as well as other counter-hormones such cortisol, epinephrine, norepinephrine and growth hormone during hypoglycemic clamp (blood glucose level, 2.5 mmol/L) before and after 2-week study treatment. The increase in plasma glucagon levels during the hypoglycemic clamp tests was not affected by DPP-4i linagliptin or GLP-1RA liraglutide treatment. The increases in growth hormone, cortisol and norepinephrine during the hypoglycemia clamp tests were significantly suppressed by DPP-4i linagliptin with a similar non-significant trend for GLP-1RA liraglutide treatment. We conclude that the glucagon response to hypoglycemia was not affected by linagliptin or liraglutide in Japanese subjects with type 2 diabetes whereas sympatho-adrenal responses to hypoglycemia were suppressed.

Supported By: Nippon Boehringer Ingelheim Co., Ltd.; Eli Lilly and Company

1158-P

Serotonin Transporter Promoter Polymorphism and Gastrointestinal Intolerance to Metformin

TANJA DUJIC, KAIXIN ZHOU, COLIN N.A. PALMER, EWAN R. PEARSON, *Dundee, United Kingdom*

The pathophysiological mechanism for gastrointestinal (GI) intolerance associated with Metformin treatment is unclear. We have recently shown that reduced-function alleles of organic cation transporter 1 (OCT1), and treatment with OCT1-inhibiting medications, are associated with intolerance to Metformin in patients with type 2 diabetes. A recent study showed that among others, serotonin transporter (SERT) may be involved in absorption of Metformin from the gut. Considering the role of serotonin in GI physiology, we investigated the influence of a common tri-allelic 5-HTTLPR polymorphism in SERT gene (*SLC6A4*) on Metformin intolerance, and explored its potential interaction with OCT1 variants. The effect of composite 5-HTTLPR/rs25531 genotypes, L^*L^* (L_AL_A), L^*S^* (L_AL_G, L_AS), and S^*S^* (SS, SL_G, L_GL_G), on Metformin intolerance was assessed in 1,356 fully tolerant and 164 Metformin-intolerant patients. The number of S^* alleles was significantly associated with higher odds of Metformin intolerance in the logistic regression model (OR=1.31, 95% CI 1.02-1.67, P=0.031). Furthermore, there was an interaction between OCT1 and SERT genotypes (P=0.003). When patients were stratified according to SERT genotypes, the presence of two deficient OCT1 alleles was associated with over a nine-fold higher odds of Metformin intolerance (OR=9.25, 95% CI 3.18-27.0, $P<10^{-4}$) in individuals with L^*L^* genotype, with a smaller effect in L^*S^* carriers (OR=2.11, 95% CI 0.99-4.50, P=0.054) and no effect in the S^*S^* genotype group (OR=0.45, 95% CI 0.09-2.20, P=0.325). Our results suggest that mechanism of Metformin GI adverse effects could be related to impaired intestinal serotonin uptake. These findings could have further clinical implication as serotonin pathway may be explored as a potential target for reducing GI intolerance to Metformin.

Supported By: Wellcome Trust UK

1159-P

The Novel Antidiabetic Drug Candidate MTBL0036 Is a Potent Inhibitor of Gluconeogenesis

GABRIEL BAVEREL, MARIE LUC, GÉRARD MOINET, GUY MARTIN, *Lyon, France*

An increase in gluconeogenesis is a major perturbation in type 2 diabetes. The aim of our study was to test if the small molecule MTBL0036 inhibits gluconeogenesis and, if so, to characterize its effect. For this, we have used the pyruvate tolerance test and studied lactate metabolism in isolated murine hepatocytes thanks to enzymatic and carbon 13 NMR techniques. In overnight-fasted db/db mice, a good model of type 2 diabetes, MTBL0036 (25 mg/kg, po) reduced the Area Under the Curve for glucose by 77% during a pyruvate tolerance test (n= 6 in the control and treated group). In hepatocytes isolated from overnight-fasted Swiss and db/db mice and incubated in Krebs-Henseleit medium with 5 mM L-lactate as substrate, MTBL0036 dose-dependently inhibited glucose synthesis with mean IC 50 values equal to 0.7 and 0.5 mM, respectively. The IC50s found for Metformin were much higher. In hepatocytes isolated from 24hr-fasted Swiss mice (n= 4) and incubated for 2 hrs with 5 mM L-2-^{13}C-lactate, the addition of 0.7 mM MTBL0036 reduced lactate consumption by 38% and glucose synthesis by 58%; by contrast, it increased the relative percentage (from 46 to 60%) of the C-2 converted into $^{13}CO_2$. These effects were associated with a 29% decrease in the cellular ATP level and a 25% decrease in the [beta-hydroxybutyrate]/[acetoacetate] ratio. This indicates a shift of the mitochondrial redox state towards oxidation. It is concluded that MTBL0036 is a mild uncoupler of the respiratory chain resulting in a decrease (i) in the cellular production and level of ATP, and (ii) in lactate gluconeogenesis, an ATP-dependent process. Given (i) that mitochondrial uncoupling is considered a potential breakthrough in the treatment of type 2 diabetes, (ii) its other PD and PK characteristics, and (iii) that it also inhibits lactate gluconeogenesis in isolated human and rat liver cells, MTBL0036 appears to be a very promising antidiabetic drug candidate.

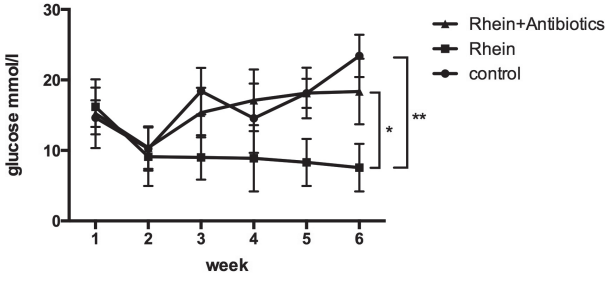
1160-P

Gut Microbiota Plays an Essential Role in the Antidiabetic Effects of Rhein

RUIFENG WANG, HONG DU, BIN LU, PING GU, HUAYING LIU, *Nanjing, China*

Rhein, an anthraquinone compound isolated from rhubarb, has been used in traditional Chinese medicine with putative antidiabetic effects. However, the mechanism remains unknown. Here, we demonstrate that rhein has the anti-hyperglycemic effect as well as the secretive function of enteroendocrine peptides through modulating the composition of the gut microbiota. Oral administration of rhein for 6 weeks could significantly reduce fasting blood glucose (FBG) level ($p<0.01$) and elevate plasma glucagon-like peptide 1 (GLP-1) level ($p<0.05$) in db/db mice without affecting glucose in db/m mice. In addition, the abundance of the bacteroidetes were increased while the firmicutes were decreased in mice treated with rhein. Whereas the antidiabetic effects of rhein could be abrogated in the db/db mice treated with broad-spectrum antibiotics before rhein treatment. Taken together, our results indicate that modulation of the gut microbiota (by the decreased Firmicutes-to-Bacteroidetes ratios) plays essential role in the antidiabetic effects of rhein, thereby suggesting a new mechanism for the therapeutic effect of rhein in diabetes.

Figure. Rhein Improves Glucose Homeostasis via Gut Microbiota in db/db Mice.



Supported By: National Natural Science Foundation of China

1161-P

Real-World (RW) Glycemic Control and Medication Adherence among Patients with Type 2 Diabetes Mellitus (T2DM) Initiated on Canagliflozin

RAHUL JAIN, JENNIFER CAI, AN-CHEN FU, WING CHOW, HIANGKIAT (JASON) TAN, *Andover, MA, Raritan, NJ, Wilmington, DE*

The safety and efficacy of canagliflozin (CANA) has been established in randomized controlled trials (RCTs). In addition to RCTs, it is important to understand the RW effectiveness of CANA. This study evaluated the impact of CANA use on A1c control among patients with T2DM over 12 months. Adherence to CANA and use of background anti-hyperglycemic agents (AHA) before and after the first CANA claim were also assessed. Adult patients with T2DM who received the first CANA claim (index date) between 4/1/13-4/30/14 with continuous enrollment for 12 months before (baseline) and

For author disclosure information, see page A696.

after (follow up) the index date were identified from HealthCore Integrated Research Database. Exclusion criteria included: a diagnosis of type 1 diabetes, pregnancy, gestational or steroid induced diabetes or exclusive use of insulin during the baseline period. Change in A1c was calculated as the difference from baseline result and the last result in the follow up. Adherence (proportion of days covered, PDC; medication possession Ratio, MPR), and number of background AHA classes before and after the index date were assessed. Study included a total of 881 patients (mean age: 55 years; 40% female; geographic regions: West (21%), Northeast (17%), Midwest (17%), South (45%)). The baseline mean (95% CI) A1c (%) was 8.4 (8.3, 8.5) with a decline of 0.8% (0.7, 0.9) observed during follow up. Among patients with baseline A1c ≥ 7% (84%), the decline was 1.0% (0.9, 1.1). The mean (median) PDC and MPR were 71% (83%) and 76% (88%), respectively; results were similar for those with baseline A1c ≥ 7%. The mean (median) number of background AHA used during baseline was 2.5 (3.0) and in the follow up period was 2.3 (2.0). This 12-month RW study of a diverse population showed a significant decline in A1c after CANA claim. The majority of CANA patients were adherent (PDC and MPR ≥80%) and a decline in background AHA use was observed. These findings complement the emergent body of RW evidence on the effectiveness of CANA.

Supported By: Janssen Scientific Affairs, LLC

1162-P

Hepatic Safety and Efficacy of LY2409021, a Novel Selective Glucagon Receptor Antagonist, in Patients with T2D as an Add-on Treatment to Metformin and Sulfonylurea

CRISTINA B. GUZMAN, MICHELLE X. ZHANG, SUDHA S. SHANKAR, RONG LIU, PARAG GARHYAN, SREEKUMAR G. PILLAI, CHRISTOF M. KAZDA, ARIE REGEV, NAGA CHALASANI, THOMAS A. HARDY, *Indianapolis, IN, Toronto, ON, Canada, Neuilly, France*

LY2409021 (LY) is a novel selective glucagon receptor antagonist. In this 6-month Phase 2, double-blind, placebo (PL)-controlled study, a longitudinal assessment of changes in absolute hepatic fat fraction (HFF) using serial magnetic resonance imaging (MRI) was performed. Patients with T2D (n=174) were randomized 3:2:3 to LY, sitagliptin (SITA), or PL, respectively. Key safety and efficacy parameters were HFF (primary endpoint: HHF at 6 mo), liver aminotransferases, fasting glucagon, lipids, blood pressure, and HbA1c. LY but not SITA or PL showed a statistically significant increase from baseline in mean absolute HFF. LY led to ALT, AST, and glucagon elevations. No subjects met Hy's law criteria or demonstrated signs of liver injury. A significant increase in mean SBP and a numeric increase in DBP from baseline were observed for LY without significant change in pulse rate. LY showed significant HbA1c reductions vs. PL but not SITA. Treatment with LY was associated with significant increases from baseline in body weight and total cholesterol vs. PL. The effects of LY on all parameters were reversible after 4 mo discontinuation. LY demonstrated modest efficacy and several adverse metabolic effects in patients with T2D who were not well controlled on MET and SU. These results do not support further development of the compound as a treatment for T2D.

Table. Results at Baseline, 6 Months, and Change from Baseline.

	LY	SITA	PL
HFF			
Baseline, % (mean±SD)	12.98±8.54 (n=62)	14.75±9.38 (n=39)	11.47±8.78 (n=67)
Change from baseline, adjusted mean (95% CI)	3.65 (2.13, 5.17) (n=50)	−0.07 (−1.94, 1.79) (n=30)	−0.79 (−2.28, 0.70) (n=50)
LY versus comparator, adjusted mean (95% CI)		3.72 (1.59, 5.85)*	4.44 (2.60, 6.28)*
ALT			
Baseline, U/L (mean±SD)	28.1±14.4 (n=65)	31.6±19.7 (n=41)	23.9±14.1 (n=68)
Change from baseline, adjusted mean (95% CI)	9.4 (4.6, 14.2) (n=57)	2.6 (−3.1, 8.3) (n=38)	−1.3 (−6.0, 3.4) (n=57)
LY versus comparator, adjusted mean (95% CI)		6.8 (0.3, 13.2)*	10.7 (5.0, 16.4)*
AST			
Baseline, U/L (mean±SD)	23.7±13.4 (n=65)	26.0±13.5 (n=41)	20.1±8.5 (n=68)
Change from baseline, adjusted mean (95% CI)	7.1 (3.3, 10.9) (n=56)	4.8 (0.2, 9.4) (n=37)	−0.4 (−4.2, 3.3) (n=57)
LY versus comparator, adjusted mean (95% CI)		2.3 (−3.0, 7.7)	7.6 (2.8, 12.3)*
HbA1c			
Baseline, % (mean±SD)	8.12±0.98 (n=65)	8.25±0.91 (n=41)	8.26±0.86 (n=68)
Change from baseline, adjusted mean (95% CI)	−0.63 (−0.94, −0.32) (n=55)	−0.42 (−0.80, −0.05) (n=35)	0.15 (−0.15, 0.45) (n=54)
LY versus comparator, adjusted mean (95% CI)		−0.20 (−0.66, 0.25)	−0.77 (−1.17, −0.38)*
Fasting Glucagon			
Baseline, pmol/L (mean±SD)	16.50±8.31 (n=64)	17.21±10.11 (n=41)	12.75±5.56 (n=68)
Change from baseline, adjusted mean (95% CI)	44.06 (36.36, 51.76) (n=57)	3.38 (−5.64, 12.41) (n=38)	5.05 (−2.50, 12.60) (n=61)
LY versus comparator, adjusted mean (95% CI)		40.68 (31.17, 50.19)*	39.01 (30.58, 47.44)*
Total Cholesterol			
Baseline, mmol/L (mean±SD)	4.535±0.961 (n=65)	4.66±0.850 (n=41)	4.672±1.101 (n=68)
Change from baseline, adjusted mean (95% CI)	0.468 (0.222, 0.714) (n=58)	0.006 (−0.282, 0.295) (n=38)	0.130 (−0.110, 0.371) (n=60)
LY versus comparator, adjusted mean (95% CI)		0.462 (0.153, 0.771)*	0.338 (0.065, 0.611)*
Body Weight			
Baseline, kg (mean±SD)	94.15±22.49 (n=65)	93.99±20.89 (n=41)	85.73±17.85 (n=68)
Change from baseline, adjusted mean (95% CI)	1.16 (0.44, 1.88) (n=58)	−0.23 (−1.10, 0.64) (n=38)	−0.08 (−0.79, 0.63) (n=61)
LY versus comparator, adjusted mean (95% CI)		1.38 (0.37, 2.39)*	1.24 (0.35, 2.13)*
Systolic BP			
Baseline, mm Hg (mean±SD)	126.4±13.3 (n=65)	128.2±11.4 (n=41)	125.8±12.3 (n=68)
Change from baseline, adjusted mean (95% CI)	6.1 (2.7, 9.5) (n=58)	1.1 (−2.9, 5.2) (n=36)	1.8 (−1.5, 5.1) (n=61)
LY versus comparator, adjusted mean (95% CI)		4.9 (0.5, 9.4)*	4.3 (0.4, 8.2)*

*p<.05
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; HFF = hepatic fat fraction.
Patient population used for analyses:
HFF: modified intent-to-treat population but excluded data after use of rescue therapy
ALT, AST, total cholesterol, fasting glucagon, body weight, and systolic BP: intent-to-treat population.
HbA1C: intent-to-treat population but excluded data after use of rescue therapy.

Supported By: Eli Lilly and Company

1163-P

Changes in Postprandial Glycemic Excursion as Mediated by Glucotoxicity Elimination with SGLT2 Inhibitor Therapy

YUKIKO TANIGUCHI, TETSURO ONISHI, YUTAKA MORI, *Tokyo, Japan, Chiba, Japan, Komae, Japan*

Objective: We investigated how improvement of hyperglycemia with SGL2 inhibitors may affect postprandial glycemic excursion by restoring postprandial insulin response through glucotoxicity elimination.

Patients and Methods: A total of 19 type 2 diabetic patients admitted for glycemic control (age, 61±9; BMI, 28±4; urinary C-peptide, 78±55 μg/day) received the SGLT2 inhibitor ipragliflozin (IPRA) 50 mg/day alone (n=9) or as add-on to conventional therapy (n=10) and were compared for diurnal glycemic variability at baseline and 2 weeks after treatment with IPRA, based on assessment of the following CGM parameters: 24-hour mean glucose; indices for 24-hour glycemic variability (SD of glucose and MAGE); incremental area under the 4-hour glucose curve (glucose $\Delta AUC_{0\text{-}4}$) following breakfast. Using the median C-peptide excretion value at admission (68μg/day) as the cut-off, the patients were divided into those above the cut-off (n=10) and those below (n=9). Statistical analyses were performed using paired t test.

Results: Following treatment with IPRA, significant decreases were seen in both groups in 24-hour mean glucose compared to baseline (P<0.01). On the other hand, while significant decreases were seen in glucose ΔAUC following breakfast as well as in the indices for glycemic variability among those above the cut-off (P<0.01), no significant decreases were seen in glucose ΔAUC following breakfast or in the indices for glycemic variability among those below.

Conclusions: Study results suggested that improvement of hyperglycemia with IPRA led through glucotoxicity elimination to recovery of postprandial bolus insulin response thus reducing postprandial glycemic excursions among those with relatively intact endogenous insulin-secretory capacity, but did not lead to recovery of postprandial bolus insulin secretion thus failing to affect postprandial glycemic excursions among those with impaired endogenous insulin-secretory capacity.

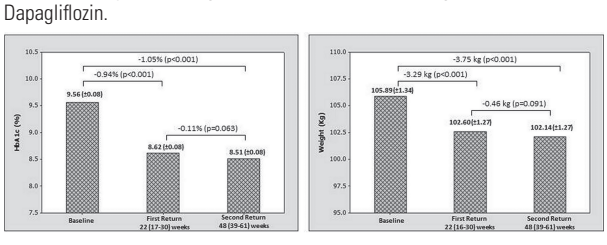
1164-P

HbA1c, Weight, Body Mass Index (BMI), and Systolic Blood Pressure Response to Dapagliflozin: The Association of British Clinical Diabetologists Nationwide Dapagliflozin Audit

MAHENDER YADAGIRI, PIYA SEN GUPTA, ADELE KENNEDY, TERENCE PANG, JAMES CLARK, HAFSA PATHAN, PHILLIP C. JOHNSTON, RICHARD CHUDLEIGH, ANTHONY ROBINSON, IAN W. GALLEN, KAREN A. ADAMSON, ROBERT E.J. RYDER, *Birmingham, United Kingdom, Antrim, United Kingdom, Dudley, United Kingdom, Surrey, United Kingdom, Belfast, United Kingdom, Swansea, United Kingdom, Bath, United Kingdom, Reading, United Kingdom, Livingston, United Kingdom*

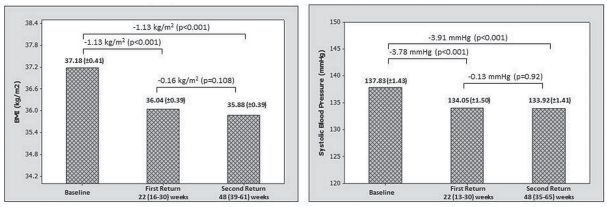
In our audit of dapagliflozin in real clinical use, between October 2014 and December 2015, 147 contributors from 57 centres submitted data on 1725 patients (56.5% males, mean (±SD) age 57.3 (±9.3) years, weight 105.9 (±23.2) kg, BMI 37.0 (±6.8) kg/m^2 and HbA1c 9.5 (±1.4)%), median (interquartile range) duration of diabetes 9.7 (3.0-14.0) years. We evaluated the metabolic response to dapagliflozin in real clinical practice in UK patients with type 2 diabetes. Those with baseline, 1st and 2nd return HbA1c (n=317) within a median (interquartile range) of 48.0 (39.0-61.0) weeks were included in this analysis. At commencement of dapagliflozin, their diabetes medications included 80.4% Metformin, 26.1% insulin (11.0% basal insulin, 12.3% basal bolus, 2.8% insulin mixtures), 29.0% sulphonylurea, 25.5% GLP-1 receptor analogues, 12.4% DPP-4 inhibitors, 5.9% pioglitazone and 1.5% other agents. By first return visit dapagliflozin reduced HbA1c, weight, BMI and systolic blood pressure by clinically and statistically significant amounts and these improvements were sustained through to the second follow up visit and indeed they increased, though not by statistically significant amounts (Figure). The improvements applied in a wide range of real-world UK patients with type 2 diabetes on a wide variety of diabetes medications.

Figure. Mean (±SE) HbA1c (N=317), Weight (N=301), BMI (N=288) and Systolic Blood Pressure (N=181), Baseline vs. First and Second Return (After Median (Interquartile Range) Weeks)) to Clinic Following Commencement of Dapagliflozin.



ADA-Supported Research Moderated Poster Discussion

For author disclosure information, see page A696.



Supported By: Association of British Clinical Diabetologists

1165-P

Canagliflozin Prescribing Patterns in a Specialty Diabetes Clinic

JUNE F. JOHNSON, RAHUL PARSA, ROBERT BAILEY, HALEY KESSINGER, *Des Moines, IA, Ames, IA, Titusville, NJ*

Limited real-world evidence exists for type 2 diabetes mellitus (T2DM) patients treated with canagliflozin in a diabetes clinic. Study goals were to examine canagliflozin prescribing and outcomes in T2DM patients managed in a diabetes clinic, the Iowa Diabetes and Endocrinology Center (IDEC). Primary outcome was change in A1c from baseline. Other outcomes included change in weight and blood pressure.

This retrospective record review was approved by the Mercy Medical Center IRB. T2DM patients prescribed canagliflozin at IDEC from 6/2013 to 6/2015 were reviewed. Patients were included if they were adults with T2DM, received care and an initial canagliflozin prescription at IDEC, and returned for ≥1 follow-up visit. Paired t-tests were used to assess changes in A1c, weight, and blood pressure. For other outcomes, summary statistics were examined.

A total of 857 patients were prescribed canagliflozin. After exclusions, 462 were evaluable at baseline, 461 at 1st follow-up, and 361 at 2nd follow-up. Mean age was 55 years, with 60% male. Mean duration of diabetes at baseline was 12.7 years and mean baseline A1c was 8.84%. At baseline, mean values for weight and key biomarkers were: weight 252 lbs; BMI 38.23 kg/m^2; systolic blood pressure (SBP) 123 mm Hg; diastolic blood pressure (DBP) 75 mm Hg; serum creatinine 0.91 mg/dL. Mean number of antihyperglycemic agents on the date of the baseline office visit was 3.6.

Mean time to 1st and 2nd follow-up was 106 and 215 days, respectively. Mean duration of canagliflozin prescribing was 10.7 months. Mean A1c at 1st and 2nd follow-up was 7.78% and 7.75%, a reduction of 1.06% and 1.09%, respectively (p<0.0001 for both). At 1st and 2nd follow-up, weight decreased by 2.01% and 1.83% (p<0.0001), SBP decreased 3.2% and 2.4%, and DBP decreased 2.59% and 2.16% (p=0.0002 for both SBP and DBP).

Canagliflozin was associated with a clinically meaningful reduction in A1c, and reductions in weight and blood pressure in a real-world setting of a diabetes clinic.

Supported By: Janssen Scientific Affairs, LLC

1166-P

Dapagliflozin (DAPA) in Patients with Type 2 Diabetes (T2D) and Mixed Dyslipidemia

HAROLD E. BAYS, PETER SARTIPY, JOHN XU, ANNA MARIA LANGKILDE, C. DAVID SJÖSTRÖM, *Louisville, KY, Gothenburg, Sweden, Gaithersburg, MD*

T2D and dyslipidemia are major cardiovascular (CV) risk factors. DAPA, a selective SGLT2 inhibitor, improves glycemic control by reducing renal glucose reabsorption, and lowers systolic blood pressure (SBP) and weight in patients with T2D. Although a large DAPA CV outcome study is ongoing, a meta-analysis of existing clinical trials suggests no increased risk of CV events with DAPA, consistent with the effects of SGLT2 inhibitors on CV risk factors. This *post hoc* analysis of 10 placebo-controlled 24-week studies evaluated the efficacy and safety of DAPA 10 mg (N=2237) or placebo (N=2164) in patients with or without mixed dyslipidemia (defined as high triglycerides [TG ≥150 mg/dL] + low HDL-C levels [Men <40 mg/dL; Women <50 mg/dL)]. Overall, 31% (1362/4401) of patients had mixed dyslipidemia. DAPA reduced HbA1c, weight, waist circumference, SBP and fasting plasma glucose in patients with and without mixed dyslipidemia, with similar effects on fasting lipid levels in both groups (Table). DAPA was associated with minor statistical changes in LDL-C, non-HDL-C, and HDL-C in both groups, and a very mild statistical decrease in TG levels in those without mixed dyslipidemia. DAPA was efficacious and well tolerated regardless of dyslipidemia status. The clinical significance of these mild lipid changes is unclear, especially in view of the effects of DAPA on other CV risk factors, and await the results of ongoing CV outcomes trials.

Table. Mean Fasting Lipid Levels at Baseline and 24 Weeks.

	Mixed dyslipidemia			Non-mixed dyslipidemia		
	n (placebo/ DAPA)	Placebo	DAPA 10 mg	n (placebo/ DAPA)	Placebo	DAPA 10 mg
		Baseline / 24 weeks	Baseline / 24 weeks		Baseline / 24 weeks	Baseline / 24 weeks
LDL-C, mg/dL	517/622	104.7 (40.3)/ 104.0 (39.2)	101.8 (39.3)/ 105.5 (40.1) *	1146/ 1234	100.1 (37.0)/ 99.3 (37.4)	100.9 (37.7)/ 103.5 (38.6) *
Non-HDL-C, mg/dL	521/625	153.9 (42.7)/ 149.3 (43.5)	153.0 (44.8)/ 152.7 (47.6) *	1154/ 1243	128.0 (43.0)/ 129.1 (44.2)	129.0 (44.5)/ 131.9 (43.6) *
Triglycerides, mg/dL	519/625	258.6 (133.6)/ 242.0 (149.4)	274.4 (174.8)/ 255.7 (208.8)	1145/ 1236	140.5 (78.5)/ 153.9 (129.2)	144.3 (141.1)/ 143.7 (80.9) *
HDL-C, mg/dL	522/625	36.9 (5.9)/ 39.5 (7.9)	36.0 (6.2)/ 39.4 (7.7) *	1154/ 1243	49.3 (10.9)/ 49.7 (11.6)	49.6 (11.8)/ 51.8 (12.2) *

*p<0.05. Data are mean (SD). Excludes data after rescue. n is the number of patients with non-missing baseline and week 24 values. p-value indicates significant differences in adjusted mean percent changes from baseline in lipid values (placebo vs. DAPA 10mg). DAPA, dapagliflozin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

Supported By: AstraZeneca

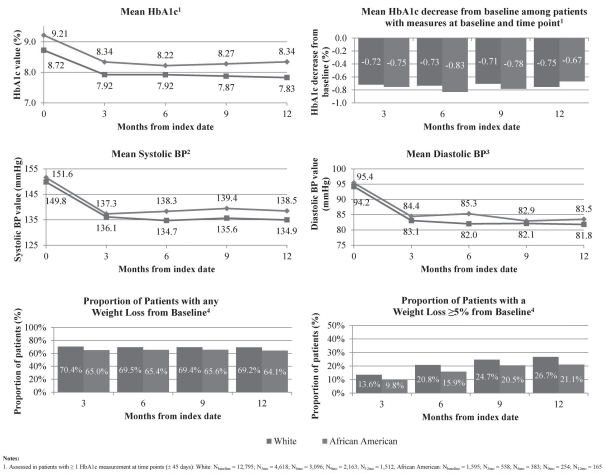
1167-P

Real-World Impact of Canagliflozin on Glycemic Control, Body Weight, and Blood Pressure in Whites and African Americans with Type 2 Diabetes Mellitus (T2DM)

PATRICK LEFEBVRE, WING CHOW, DOMINIC PILON, BRUNO EMOND, MARIE-HÉLÈNE LAFEUILLE, MICHAEL PFEIFER, MARCIA F.T. RUPNOW, MEI SHENG DUH, *Montreal, QC, Canada, Raritan, NJ, Boston, MA*

Canagliflozin (CANA), a sodium glucose co-transporter 2 inhibitor, has been shown to improve HbA1c, body weight (BW), and blood pressure (BP) in patients with T2DM in clinical trials. Real-world evidence on CANA are emerging, although race-specific data are not available to-date. This study assessed HbA1c, BW, and BP among whites and African Americans (AAs) with T2DM receiving CANA in clinical practice. White and AA adults with T2DM and ≥12 months of clinical activity (baseline) before first CANA prescription (index) were identified in the Cegedim Strategic Data U.S. electronic health records dataset. Outcomes were evaluated at 3, 6, 9, and 12 months post-index among uncontrolled patients at baseline (HbA1c ≥7%, systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, all patients for BW). Among patients initiated on CANA, 22,657 were white and 2,551 were AA. At index, CANA 300MG was prescribed for 36% of patients and respectively 88% and 67% used antihyperglycemics or antihypertensives at baseline. Patients in both groups had improvements in HbA1c, BW, and BP 3 months after initiation of CANA and these means and proportions were maintained through 12 months (Figure). Despite different clinical profiles at initiation of CANA, whites and AAs had improvements in diabetes-related quality measures; means and proportions were maintained through 12 months post-index.

Figure. Evolution of Quality Measures During the 12-Month Follow-up.



Notes:
1. Assessed in patients with ≥ 1 HbA1c measurement at time points (± 45 days). White: $N_{baseline}$ = 12,795; N_{3m} = 4,618; N_{6m} = 3,096; N_{9m} = 2,163; N_{12m} = 1,512. African American: $N_{baseline}$ = 1,595; N_{3m} = 558; N_{6m} = 383; N_{9m} = 254; N_{12m} = 165
2. Assessed in patients with ≥ 1 systolic BP measurement at time points (± 45 days). White: $N_{baseline}$ = 5,541; N_{3m} = 2,753; N_{6m} = 1,908; N_{9m} = 1,279; N_{12m} = 972. African American: $N_{baseline}$ = 772; N_{3m} = 343; N_{6m} = 256; N_{9m} = 167; N_{12m} = 113
3. Assessed in patients with ≥ 1 diastolic BP measurement at time points (± 45 days): White: $N_{baseline}$ = 2,054; N_{3m} = 947; N_{6m} = 655; N_{9m} = 434; N_{12m} = 327. African American: $N_{baseline}$ = 384; N_{3m} = 164; N_{6m} = 118; N_{9m} = 79; N_{12m} = 53
4. Assessed in patients with ≥ 1 weight measurement at baseline and time point (± 45 days): White: N_{3m} = 10,918; N_{6m} = 7,723; N_{9m} = 5,203; N_{12m} = 3,792. African American: N_{3m} = 1,137; N_{6m} = 832; N_{9m} = 541; N_{12m} = 365

Supported By: Janssen Scientific Affairs, LLC

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1168-P

Quality Measure Outcomes with Dapagliflozin (DAPA) Add-on to Metformin (MET) or Insulin (INS) in Patients with Type 2 Diabetes (T2D)

TRACI MANSFIELD, KELLY BELL, GEOFFREY REZVANI, ALLA SHATSKOV, JOHN J. SHEEHAN, *Fort Washington, PA*

Diabetes quality measures evaluate the performance of clinical care. Current measures include achievement of A1c <7%, <8%, or >9%, blood pressure (BP) <140/<90 mmHg, and in patients with body mass index (BMI) ≥25 kg/m^2, weight loss of ≥4.5 kg. Two post hoc analyses of 24-wk clinical trial data for DAPA 5 or 10 mg/d add-on to MET or INS vs. placebo (PBO) add-on were performed to determine the effect of DAPA on achievement of quality measure goals. Patients in the add-on to MET analysis had lower mean A1c at baseline (7.2%-8.2%) and shorter mean T2D duration (5.5-6.4 y) than those in the add-on to INS analysis (mean A1c: 8.5%-8.6%; mean T2D duration: 13.1-14.2 y). As add-on to MET or INS, DAPA increased the proportion of patients achieving glycemic thresholds (Table). A significant effect on achievement of BP <140/<90 mmHg was observed with DAPA add-on to MET. More patients with baseline BMI ≥25 kg/m^2 lost ≥4.5 kg with DAPA add-on to MET (*P*<0.001, each dose) or INS (*P*<0.01, DAPA 10 mg only) vs. PBO add-on. DAPA add-on to MET or INS also significantly increased the proportion of patients who achieved the composite outcome of A1c <8% and BP <140/<90 mmHg (*P*<0.01 each dose vs. PBO add-on); the achievement of A1c <7% and BP <140/<90 mmHg was inconsistent. In conclusion, DAPA add-on to MET or INS increased the proportion of patients achieving diabetes quality measures compared with PBO add-on.

Figure. Quality Measure Outcomes with DAPA Add-on at 24 Weeks.

	Add-on to Metformin†			Add-on to Insulin‡		
End points	PBO (n=228) % meeting threshold*	DAPA 5 mg (n=137) % meeting threshold *P* value*	DAPA 10 mg (n=224) % meeting threshold *P* value*	PBO (n=193) % meeting threshold*	DAPA 5 mg (n=211) % meeting threshold *P* value*	DAPA 10 mg (n=194) % meeting threshold *P* value*
A1C <7% (good glycemic control)	34.7	35.3 *P*=0.909	53.6 *P*<0.001	9.0	19.0 *P*=0.006	20.8 *P*=0.001
A1C <8% (good glycemic control)	73.8	73.7 *P*=1.000	89.5 *P*<0.001	42.0	64.8 *P*<0.001	67.2 *P*<0.001
A1C >9% (poor glycemic control)	9.3	5.3 *P*=0.222	2.3 *P*=0.002	20.2	7.6 *P*<0.001	6.8 *P*<0.001
BP <140/<90 mmHg	66.5	86.9 *P*<0.001	81.0 *P*<0.001	66.7	66.5 *P*=1.000	64.6 *P*=0.745
Baseline BMI ≥25 kg/m^2 who lost ≥4.5 kg	6.5	26.4 *P*<0.001	25.7 *P*<0.001	3.4	8.6 *P*=0.051	10.6 *P*=0.008
A1C <7% and BP <140/<90 mmHg	24.9	28.6 *P*=0.458	43.4 *P*<0.001	7.5	14.8 *P*=0.026	10.9 *P*=0.289
A1C <8% and BP <140/<90 mmHg	49.3	64.7 *P*=0.006	72.1 *P*<0.001	30.1	44.0 *P*=0.005	46.4 *P*=0.001

*Data are proportion of patients in each treatment group meeting threshold (%), based on number of patients with non-missing values and *P* value for difference vs PBO based on Fisher's exact test; †Pooled analysis of 2 studies of DAPA add-on to MET vs PBO add-on (NCT00528879, NCT00855166); ‡Single study of DAPA add-on to INS (± up to 2 other oral antidiabetes drugs) vs PBO add-on (NCT00673231).

Supported By: AstraZeneca

1169-P

Efficacy and Safety of Gemigliptin as Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin and Glimepiride

KYUNG AH HAN, JAE MYUNG YU, HAK CHUL JANG, KYU JEUNG AHN, TAKKEUN OH, HYOUNG WOO LEE, DAEHO LEE, JAE TAEK KIM, TAE SUN PARK, JOO YOUNG NAM, CHOON HEE CHUNG, BYUNG-JOON KIM, SEOK WON PARK, SUNG-HO KIM, KYONG SOO PARK, *Seoul, Republic of Korea, Cheongju, Republic of Korea, Daegu, Republic of Korea, Iksan, Republic of Korea, Jeonju, Republic of Korea, Ilsan, Republic of Korea, Wonju, Republic of Korea, Incheon, Republic of Korea, Seongnam, Republic of Korea*

Gemigliptin is a potent, selective, competitive, and long-acting dipeptidyl peptidase (DPP)-4 inhibitor. This study evaluated the efficacy and safety of gemigliptin as add-on therapy to Metformin and glimepiride for 24 weeks compared with placebo in patients with type 2 diabetes mellitus (T2DM) inadequate glycemic control. In this multicenter, randomized, double-blind, Phase III study, eligible patients with inadequate glycemic control (7% ≤ HbA1c ≤ 11%) were randomized to gemigliptin 50 mg q.d (n=109) or placebo (n=110). The primary endpoint was change from baseline in HbA1c after 24 weeks. Baseline demographics were similar between groups (age 60.9 years; BMI 24.9 kg/m^2, duration of T2DM 12.9 years), with mean ± SD baseline HbA1c of 8.12 ± 0.82% in the gemigliptin group and 8.15 ± 0.89% in the placebo group. At week 24, adjusted mean ± SE change HbA1c with gemigliptin was -0.88 ± 0.17% (change with placebo -0.01 ± 0.18%; difference -0.87 ± 0.12%, 95% CI -1.09 to -0.64; p<0.0001). The differences in proportions achieving an HbA1c <7 or <6.5% were also statistically significant (p<0.0001) between groups. Gemigliptin was generally well tolerated, although there was a higher incidence of overall adverse events (AEs) in the gemigliptin group than in the placebo group (56.1% and 36.0%, respectively). Drug-related AEs were reported for 3.7% and 2.7% of gemigliptin and placebo, respectively. Hypoglycemia occurred in 9.4 and 2.7% of the gemigliptin and placebo groups, respectively.In conclusion, triple therapy with gemigliptin 50 mg q.d in patients with T2DM inadequately controlled on Metformin and glimepiride improved glycemic control and was generally well tolerated over 24 weeks.

1170-P

The Glycemic Response to Dapagliflozin According to Intensity of Background Diabetes Treatment or Duration of Type 2 Diabetes: The Association of British Clinical Diabetologists Nationwide Dapagliflozin Audit

KEN Y. THONG, MAHENDER YADAGIRI, PIYA SEN GUPTA, PETER WINOCOUR, MAMTA JOSHI, JOHN WILDING, JEFFREY W. STEPHENS, STEPHEN C. BAIN, ANTHONY ROBINSON, IAN W. GALLEN, KAREN ADAMSON, ROBERT E.J. RYDER, *Perth, Australia, Birmingham, United Kingdom, Welwyn Garden City, United Kingdom, London, United Kingdom, Liverpool, United Kingdom, Swansea, United Kingdom, Bath, United Kingdom, Reading, United Kingdom, Livingston, United Kingdom*

Our nationwide audits of GLP-1 receptor agonists revealed they were less effective in patients with more advanced type 2 diabetes. We investigated whether the glycaemic response to dapagliflozin would differ according to the intensity of background diabetes treatment or duration of disease.

Data was obtained from an audit database analysing the use of dapagliflozin in clinical practice in the UK. Between October 2014 and December 2015, 57 centres submitted data on 1720 patients. For this analysis, patients were stratified for receipt to none, one, two or three background diabetes therapies (oral therapies or GLP-1 receptor agonists), or insulin, or for diabetes duration of 0-5, 6-10, or >10 years. Changes in HbA1c at 26 weeks of treatment were compared across groups after adjusting for baseline HbA1c and renal function.

There were 718 patients with the relevant data analysed. Mean (±SD) baseline HbA1c and BMI were 9.6±1.4% and 33.4±17.5 kg/m^2 with 22.0% of patients on GLP-1 receptor agonists and 38.4% on insulin. Patients on no background therapy (n=32), one drug therapy (n=139), two therapies (n=173), three therapies (n=98) and insulin (n=276) achieved adjusted mean HbA1c changes (±SEM) of -0.9 ± 0.2%, -1.1 ± 0.1%, -1.2 ± 0.1%, -1.2 ± 0.1% and -0.9 ± 0.1%, respectively (p=0.021 for effect of treatment group). Patients on insulin achieved lower HbA1c reduction compared with patients on two therapies (difference [95% CI]; 0.3% [0.03, 0.61], p=0.024). Adjusted mean HbA1c changes were -1.1 ± 0.1% for patients with diabetes duration 0-5 years (n=183), -1.1 ± 0.1% for 6-10 years (n=161) and -1.0 ± 0.1% for >10 years (n=268) (p=0.47 for effect of diabetes duration).

Dapagliflozin should be considered comparably as effective in patients with more advanced type 2 diabetes. This is in keeping with its mechanism of action being independent of beta cell function.

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1171-P

Beneficial Effects of TM-25659 on Insulin Resistance and Hepatic Steatosis Induced by a High-Fat Diet in C57BL/6J Mice

JONG GAB JUNG, SANG-A LEE, JA YOUNG JEON, SUNG-E CHOI, YUP KANG, MYUNG AE BAE, JIN HEE AHN, HANA JEONG, EUN SOOK HWANG, SEUNG JIN HAN, HAE JIN KIM, TAE HO KIM, DAE JUNG KIM, KWAN-WOO LEE, *Suwon, Republic of Korea, Seoul, Republic of Korea*

2-butyl-5-methyl-6-(pyridine-3-yl)-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-3H-imidazo [4,5-b] pyridine] (TM-25659), a known transcriptional coactivator with PDZ-binding motif (TAZ) activator, inhibits adipocyte differentiation by interacting with peroxisome proliferator-activated receptor gamma. Our aim was to explore the therapeutic effects of TM-25659 in the context of obesity, obesity-related inflammation, insulin-resistance, and hepatic steatosis. C57BL/6J mice were fed a normal diet (ND) or a high-fat (HF) diet for 6 weeks. The ND group continued to consume a normal diet for a further 8 weeks, whereas the HF-diet animals were randomly assigned into two subgroups who consumed an HF-diet or an HF+TM-25659 diet for a further 8 weeks. Body weight and food intake were monitored, as were glucose homeostasis and insulin-sensitivity. Fasting insulin and serum lipid levels were measured at the end of the study. Also, the transcriptional levels of genes involved in inflammation and lipid metabolism were analyzed. We also investigated the molecular mechanisms of TM-25659-mediated palmitate

(PA)-induced insulin-resistance in HepG2 cells. We measured both the extent of insulin signaling and the expression levels of inflammatory cytokines to explain the therapeutic effects of TM-25659. Mice consuming the HF+TM-25659 diet were less obese than controls, exhibited less insulin-resistance, and had lower plasma levels of inflammatory cytokines. TM-25659 also inhibited hepatic steatosis induced by the HF diet. Immunoblotting revealed that TM-25659 increased hepatic AMP-activated protein kinase (AMPK) levels. TM-25659 also reduced the liver levels of inflammatory cytokines and reduced the fall in insulin-stimulated (protein kinase B) (AKT) phosphorylation by AMPK evident in mice on the HF diet. Thus, TM-25659 may be useful to treat insulin-resistance and hepatic steatosis. The drug activated AMPK in a high fat diet-induced model of obesity.

1172-P

Effects of Linagliptin Monotherapy Compared with Voglibose on Postprandial Blood Glucose Responses in Japanese Patients with Type 2 Diabetes: Linagliptin Study of Effects on Postprandial Blood Glucose (L-STEP)

YOSHIO FUJITANI, SHIMPEI FUJIMOTO, KIYOHITO TAKAHASHI, HIROAKI SATOH, TAKAHISA HIROSE, MASUMI AI, YOSUKE OKADA, MASAHIKO GOSHO, TOMOYA MITA, HIROTAKA WATADA, *Tokyo, Japan, Nankoku, Japan, Hakodate, Japan, Fukushima, Japan, Kitakyusyu, Japan, Ibaraki City, Japan*

Aims: To compare the efficacy on glycemic parameters between a 12-week administration of once-daily linagliptin and thrice-daily voglibose in Japanese patients with type 2 diabetes.

Methods: This was a prospective, randomized, open-label, multicenter, parallel-group, comparative study. A total of 382 diabetic patients in whom blood glucose levels were inadequately controlled by diet and exercise were randomized to the linagliptin group (n=192) or the voglibose group (n=190). A meal tolerance test was performed at weeks 0 and 12. Primary outcomes were the change from baseline to week 12 in serum glucose levels at 2 hours after the start of the meal tolerance test, HbA1c levels, and serum fasting glucose levels, which were compared between the 2 groups.

Results: Whereas changes in serum glucose levels at 2 hours after the start of the meal tolerance test did not differ between the groups, the mean change in HbA1c levels from baseline to week 12 in the linagliptin group (-0.5±0.5%) was significantly larger than in the voglibose group (-0.2±0.5%). In addition, there was significant difference in changes in serum fasting glucose levels (-0.51 ± 0.95 mmol/L in the linagliptin group vs. -0.18 ± 0.92 mmol/L in the voglibose group, P<0.001). During the 12 weeks of treatments, the incidences of hypoglycemia, serious adverse events (AEs), and discontinuations due to AEs were low and similar in both groups**.** However, gastrointestinal AEs were significantly lower in the linagliptin group than in the voglibose group.

Conclusions: These data suggested that linagliptin monotherapy had a stronger glucose-lowering effect than voglibose monotherapy with respect to HbA1c and serum fasting glucose levels, but not serum glucose levels 2 hours after the start of the meal tolerance test.

1173-P

Effects of Icosapent Ethyl on Lipoprotein Particle Concentration and Size in Statin-Treated Patients with Persistent High Triglycerides: ANCHOR Patients with Diabetes Mellitus

ELIOT A. BRINTON, CHRISTIE M. BALLANTYNE, HAROLD E. BAYS, WILLIAM CROMWELL, JAMES OTVOS, SEPHY PHILIP, RALPH T. DOYLE, REBECCA A. JULIANO, *Salt Lake City, UT, Houston, TX, Louisville, KY, Raleigh, NC, Bedminster, NJ*

Icosapent ethyl (IPE; Vascepa) is a high-purity prescription form of eicosapentaenoic acid ethyl ester approved at 4 g/day as an adjunct to diet to reduce triglyceride (TG) levels in adults with TG ≥500 mg/dL. IPE's effects on lipoprotein particles have not been examined in patients with diabetes. The ANCHOR study enrolled patients at high cardiovascular risk with TG 200-500 mg/dL despite statin-induced control of low-density lipoprotein cholesterol (LDL-C). In this post-hoc analysis of ANCHOR patients with diabetes (73% of all patients), we measured lipoprotein particle concentration and size by nuclear magnetic resonance (NMR) spectroscopy and tested their correlations with plasma apolipoprotein B (ApoB) levels, which were previously shown to be significantly reduced by IPE 4 g/day (–9.5%; *P*<0.0001) in this population. NMR analysis revealed that IPE 4 g/day (n=154) significantly reduced the median concentration of: total (–11.3%; *P*=0.004), large (–48.9%; *P*<0.0001), and medium (–12.0%; *P*=0.02) very-low-density lipoprotein (VLDL) particles; total (–7.4%; *P*=0.009) and small (–13.1%; *P*<0.0001) LDL particles; and total (–7.5%; *P*<0.0001) and large (–29.7%; *P*<0.0001) high-density lipoprotein (HDL) particles vs. placebo (n=160). As these results suggest, IPE decreased median VLDL (–8.5%; *P*<0.0001) and HDL particle size (–1.2%; *P*=0.001) and increased LDL size (+0.5%; *P*=0.01). Atherogenic particle concentration (total VLDL+total LDL) decreased (–7.7%; *P*=0.003) and its correlation with plasma ApoB at baseline (R^2=0.53; *P*<0.0001) appeared to become stronger at 12 weeks (R^2=0.64 *P*<0.0001). In conclusion, in patients with diabetes mellitus at high cardiovascular risk and with persistently high TG levels on a statin, icosapent ethyl 4 g/day reduced atherogenic lipoprotein particle concentrations, correlating strongly with reduced ApoB levels.

1174-P

Target Achievement and Quality Measure (QM) Attainment with Titrated Canagliflozin (CANA) in Patients with Type 2 Diabetes Mellitus (T2DM) as Add-on to Metformin (MET) + Sitagliptin (SITA)

JOCHEN SEUFERT, NARESH AGGARWAL, ROBERT BAILEY, ANJUN CAO, ALBERT FUNG, MICHAEL PFEIFER, MARIA ALBA, HELENA W. RODBARD, *Freiburg, Germany, Brampton, ON, Canada, Raritan, NJ, Rockville, MD*

QMs are becoming increasingly important for evaluating physician performance in patient care. This post hoc analysis focused on select QMs and target achievement of glycemic and blood pressure (BP) control with CANA in a 26-week, randomized, double-blind study (N = 213) that evaluated a dose-titration protocol in triple oral therapy. T2DM patients inadequately controlled on MET + SITA were titrated from CANA 100 mg or placebo (PBO) to CANA 300 mg or matching PBO after 6 weeks if baseline eGFR was ≥70 mL/min/1.73 m^2, fasting self-monitored blood glucose was ≥100 mg/dL, and no volume depletion-related AEs within 2 weeks prior to uptitration occurred. Patients not meeting these criteria remained on CANA 100 mg or PBO and were reassessed for titration every 2 weeks through week 18. In total, 85.4% of patients uptitrated from CANA 100 to 300 mg or matching PBO (mean uptitration time 6.2 weeks). Titrated CANA significantly reduced A1c, body weight, and BP vs. PBO at 26 weeks. A greater proportion of patients achieved A1c <7.0% and <8.0% and fewer patients had A1c >9.0% with CANA vs. PBO (Table). More patients achieved BP <140/90 and <130/80 mmHg with CANA vs. PBO. CANA was generally well tolerated, with a safety profile similar to prior studies. In summary, titrated CANA showed better target achievement than PBO in T2DM patients on MET + SITA.

Table. Proportion of Patients Achieving Targets and QMs at Week 26.

	PBO (n = 106)	CANA (n = 107)	Nominal *P* value
Glycemic treatment goals			
Patients with A1C <7.0%, n (%)	10 (12.2)	31 (32.3)	
OR vs PBO (95% CI)		4.5 (1.9, 10.9)	0.001
Patients with A1C <8.0%, n (%)	32 (39.0)	68 (70.8)	
OR vs PBO (95% CI)		5.6 (2.7, 11.4)	<0.001
Patients with A1C >9.0%, n (%)	19 (23.2)	11 (11.5)	
OR vs PBO (95% CI)		0.3 (0.1, 0.6)	0.002
BP treatment goals			
Patients with BP <140/90 mmHg, n (%)	65 (78.3)	83 (86.5)	
OR vs PBO (95% CI)		2.8 (1.2, 6.5)	0.017
Patients with BP <130/80 mmHg, n (%)	27 (32.5)	52 (54.2)	
OR vs PBO (95% CI)		3.6 (1.7, 7.5)	0.001

OR, odds ratio; CI, confidence interval.

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1175-P

Response to SGLT2 Inhibitor May Be Altered in HNF1A-MODY

JERZY HOHENDORFF, MAGDALENA SZOPA, JAN SKUPIEN, TOMASZ KLUPA, MACIEJ T. MALECKI, *Krakow, Poland*

MODY accounts for 1-5% of all diabetes cases and most of them are and HNF1A- and GCK-MODY. Dietary intervention is generally sufficient to maintain good glycemic control in subjects with GCK gene mutation. HNF1A gene mutations affect insulin secretion. For patients with genetically confirmed HNF1A-MODY sulfonylurea therapy should be considered as the first-line treatment. It was shown that HNF1A controls SGLT2 (sodium-glucose co-transporter 2) expression which results in increased glycosuria in HNF1A-MODY patients. Therefore, response to SGLT2 inhibitors in HNF1A-MODY patients may be altered. In this pilot study, we aimed to assess differences in response to a single morning application of 10 mg dapagliflozin in 11 patients with GCK-MODY and 10 with HNF1A-MODY. Dapagliflozin was added to patients current treatment regimens - all GCK-MODY subjects were on diet only, whereas HNF1A-MODY patients were on diet (1), SU (6), SU combined with Metformin (2) and SU combined with 3U/d of insulin (1). Fasting plasma glucose (FPG), urine glucose concentration and urinary glucose-to-creatinine ratio (GCR) were measured in the morning of the administration day and the day after. Additionally, patients were asked to perform self-monitoring of blood glucose twice - on the administration day and the day before. There were no differences in mean HbA1c (6, 25; 6, 06%) nor BMI (23, 1; 24, 6 kg/m^2) between the groups. GCK-MODY patients

For author disclosure information, see page A696.

had higher mean FPG (6, 81 vs. 5, 66 mmol/l, p=0,0137). Mean reduction in FPG after dapagliflozin administration was 0, 63 in GCK-MODY, whereas in HNF1A-MODY patients was 0, 24 mmol/l (p=0,2367). This could suggest altered response to SGLT2 inhibitors in HNF1A-MODY due to impaired SGLT2 function. Moreover, we found a difference in median increment in GCR after SGLT2 inhibitor administration between GCK-MODY and HNF1A-MODY patients (24, 5 vs.14, 0 p=0,0447). To summarize, SGLT2 inhibitors seems to be less efficient in HNF1A-MODY than in GCK-MODY. This finding requires further studies.

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1176-P

Comparison of Diurnal Glycemic Variability on Day 1 vs. Day 7 of Treatment with the Once-Weekly DPP-4 Inhibitor Trelagliptin

TETSURO ONISHI, YUKIKO TANIGUCHI, YUTAKA MORI, *Chiba, Japan, Tokyo, Japan, Komae, Japan*

Objective: We examined whether the sustained DPP-4 inhibitory activity with trelagliptin (T) is associated with sustained glucose lowering effect from day 1 to day 7 of treatment with T.

Methods: A total of 16 type 2 diabetic outpatients with stable glycemic control after conventional therapy (HbA1c, 7.4 ± 0.7; GA, 19.0 ± 2.5; 1, 5AG, 10.0 ± 5.4) were given T 100 mg once weekly (as add-on in 14 and as switch-over from sitagliptin 50 mg/day in 2); the patients were evaluated for diurnal glycemic variability using CGM at baseline, on day 7 after 3 repeated doses, and on day 1 after 4 repeated doses. Based on CGM-derived data, the patients were compared for the following parameters: 24-hour mean glucose (mg/dl); indices for 24-hour glycemic variability [SD of glucose (mg/dl), total area for the range of glycemic variability (mg·hr/dl), MAGE (mg/dl)] They were also evaluated for HbA1c, GA, and 1, 5AG at baseline as well as on day 2 of treatment with T after 4 repeated doses. Statistical analyses were performed using paired t test.

Results: HbA1c and GA values were significantly decreased and 1, 5AG values significantly increased in the 12 patients given T as add-on (P<0.01), with significant decreases shown for their 24-hour mean glucose (P<0.01) as well as decreases, albeit non-significant, in the indices of 24-hour glycemic variability. In contrast, no significant changes were seen in the 2 patients given T as switch-over in regard to their HbA1c, GA, 1, 5AG and CGM parameters. In addition, while those given T as add-on and as switch-over were shown to be not significantly different with regard to these CGM parameters on days 1 and 7, there was a trend toward increase in these parameters on day 7 compared to those on day 1.

Conclusions: The CGM-derived data for diurnal glycemic variability with T show that its glucose-lowering effects are less likely to remain consistent over a 7-day period but are likely to be comparable to those with once-daily DPP-4 inhibitors.

1177-P

Preclinical Findings with Oral GLP-1 Receptor Agonist TTP273 Reinforce Importance of Neuro-enteroendocrine Signaling

JENNIFER L.R. FREEMAN, JOSEPH AGOLORY, CARMEN VALCARCE, *High Point, NC*

GLP-1, a well-characterized peptide hormone secreted by the L-cells of the intestine, activates GLP-1 receptors found throughout the body. Interest in GLP-1 arose from its effects in the pancreas stimulating insulin secretion and decreasing glucagon levels. More recently, additional sites of GLP-1 action, including the gut, have been identified.

The GLP-1 receptor is a well validated target for the treatment of type 2 diabetes mellitus (T2DM) and has recently been shown to be effective as a treatment for weight management in nondiabetic obese and overweight subjects. Injectable GLP-1R agonists are effective in lowering blood glucose and reducing weight and are generally safe and well tolerated except for major side effects related to GI distress (nausea and vomiting). Oral DPP-IV inhibitors that increase GLP-1 levels by preventing its degradation are also effective in lowering blood glucose and are well tolerated, but have little or no effect on weight reduction.

We report preclinical characterization of orally bioavailable, specific, non-peptide GLP-1R agonists, TTP3859 and TTP273 demonstrating they are specific GLP-1 receptor agonists in vitro, demonstrate dose dependent reductions of plasma glucose levels in vivo following an oral glucose tolerance test (OGTT) and have weight lowering effects following 14 days of dosing. In studies evaluating glucose levels following an OGTT and food intake following re-feeding, only animals dosed orally with TTP273 as opposed to those dosed intravenously, showed reduction in food intake while both routes of administration exhibited improved glycemic control, consistent with the importance of GLP-1 receptor activation in the gut to promote satiety through signaling to the brain via the vagus nerve. A Phase 2 study is currently ongoing to evaluate TTP273 administered orally in T2DM subjects to evaluate glycemic control and weight loss.

1178-P

Use of a Digital Health Offering to Optimize Therapy in Patients with Uncontrolled Type 2 Diabetes

JUAN FRIAS, JEFF UNGER, MARINA RAIKHEL, NAUNIHAL VIRDI, PRAVEEN RAJA, YOONA KIM, GEORGE SAVAGE, LARS OSTERBERG, *Los Angeles, CA, Chino, CA, Lomita, CA, Redwood City, CA, Palo Alto, CA*

Successful management of type 2 diabetes (DM) requires a multi-pronged approach of patient activation, lifestyle changes, and therapy optimization; however, about half of patients are not achieving their target A1c. Proteus Discover, a digital health offering (DH) consists of sensor-enabled medicines (directly measure adherence), a wearable sensor (records medication ingestion, activity and rest), a patient app (supports self-management, adherence, and activation), and a provider portal (facilitates therapy optimization). This abstract reports interim results of change in A1c in a pilot study investigating the potential of DH to improve outcomes in patients with uncontrolled DM and hypertension (HTN).

This IRB-approved, 12-week, cluster-randomized study enrolled non-insulin using subjects with uncontrolled DM (A1c ≥7%) and HTN (systolic blood pressure ≥140 mm Hg) treated with Metformin and/or sulfonylurea and ≥2 anti-hypertensives. Subjects received DH with sensor-enabled medications for 4 or 12 weeks (DH), or usual care (UC). Change in A1c was a secondary outcome. Additional analyses were performed examining change in A1c by baseline A1c (<8 and ≥8%). Results are summarized descriptively.

This intention-to-treat cohort included 110 subjects (mean age 59 years, 48% female, 44% Hispanic, and 56% income ≤$20,000 per year). Baseline A1c values were 8.6 ± 0.1% (DH, n=77), and 8.1 ± 0.3% (UC, n=33). All values are mean ± standard error. Changes in A1c were -0.2 ± 0.1% (DH) and 0.2 ± 0.3% (UC). In subjects with baseline A1c<8% (n = 48), baseline A1c was 7.2% ± 0.1% with an A1c change of 0.3% ± 0.2% in DH and 0.2% ± 0.3% in UC. In subjects with baseline A1c ≥8% (n = 62), baseline A1c was 9.4% ± 0.2 with an A1c change of -0.5 ± 0.1% in DH and 0.2 ± 0.3% in UC.

Interim results from this study suggest a digital health offering that supports patient self-management and activation, and aids therapy optimization facilitates improvement in glycemic control, especially in those patients whose A1c is at or above 8%.

1179-P

Effects of Dipeptidyl Peptidase-4 Inhibitors as Monotherapy or Add-on Therapy on Beta-Cell Function and Insulin Resistance in Patients with Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Clinical Trials

XIAOLIN ZHU, XIAFEI LV, BIN ZHAO, LIANG DU, DAWEI CHEN, CHUN WANG, GUANGJIAN LIU, XINGWU RAN, *Shanghai, China, Chengdu, China*

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a novel family of glucose-lowering agents that are increasingly used in clinical practice in treating patients with type 2 diabetes. Experimental data show that DPP-4 inhibitors may help preserve pancreatic beta-cell function; however, results from previous studies in humans have been inconsistent. In this study, we aimed to systematically review the available evidence and quantitatively summarize the findings by performing a meta-analysis of randomized controlled trials (RCTs). We conducted a systematic search for pertinent literature from PubMed, Embase, and Cochrane Library databases through March 2015. We identified RCTs investigating the effects of DPP-4 inhibitors as monotherapy or add-on therapy on beta-cell function or insulin resistance, as measured by the homoeostasis model assessment (HOMA-B and HOMA-IR, respectively), in patients with type 2 diabetes. We calculated weighted mean differences (WMDs) and 95% confidence intervals (CIs) for the change in HOMA indexes from baseline to the end of the trial in each of the included trials and pooled the data in the meta-analysis using a random-effects model. Forty-one trials were included in the present analysis. Compared with placebo control, DPP-4 inhibitors as monotherapy significantly improved beta-cell function (WMD 9.41; 95% CI 7.39, 11.42). Similarly, DPP-4 inhibitors as add-on therapy in combination with other drugs also significantly improved beta-cell function (WMD 10.58; 95% CI 7.20, 13.96). However, we found no significant improvement in insulin resistance after treatment with DPP-4 inhibitors as mono-therapy or as add-on therapy. In conclusion, DPP-4 inhibitors as monotherapy or as add-on therapy significantly improved beta-cell function but had no significant effect on insulin resistance among patients with type 2 diabetes.

1180-P

In Rodents, Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) Moderately Increase Blood Ketones thus Amplifying the Effects of Fasting

ERIC W. MAYOUX, JULIA FAESSLER, CARINA HERTENBERGER, MICHAEL MARK, GERD LUIPPOLD, *Biberach, Germany*

SGLT2i represent a novel class of drugs for treating type 2 diabetes with a unique mode of action. By triggering urinary glucose excretion, SGLT2i decrease blood glucose independently of the insulin pathway. SGLT2i are also reported to increase moderately glucagon, ketone bodies, hepatic glucose production and to induce a switch toward lipid utilization. However the mechanism of these effects is not yet fully understood. This study aims to investigate the pathways by which SGLT2i triggers a mild augmentation in ketones. In overnight fasted and non-fasted Sprague-Dawley (SD) rats, blood ketones have been followed over 5h after a single dose of 3 and 10 mg/kg empagliflozin (SGLT2i). Ketones level at baseline and AUC_{0-5h} were more elevated in fasted animals vs. non-fasted. Hepatic glycogen of fasted rats was fully depleted (0.25 µmol/g) while remains high (195 µmol/g) in non-fasted rats (5h time point). Only in fasted rats, in which hepatic glycogen was depleted, SGLT2i increased the ketone AUC_{0-5h} (+17 and +32%). In non-fasted animals, empagliflozin did not increase ketones, but hepatic glycogen was diminished vs. vehicle (-10 and -28%). In diabetic ZDF rats, empagliflozin increased ketones also only in fasted rats while lowering blood glucose in both groups. In SD rats that were refed after overnight fasting, SGLT2i induced a peak of ketones, which normalized to the level of the vehicle group after 5h. The augmentation of blood glucose was slower and hepatic glycogen content at 5h was lower (-55%) compared to vehicle. Further experiments showed that the peak of ketone bodies at refeeding was triggered mostly by fat, and that SGLT2i moderately increased glucagon level and lowered insulin compared to vehicle. Together our data demonstrate that SGLT2i induce a moderate elevation of ketones by amplifying the fasting phenomenon of low glucose, low insulin, higher glucagon and depletion of hepatic glycogen triggering the use of fat for hepatic ketogenesis.

1181-P

Assessing the Safety of Sitagliptin in Patients with Type 2 Diabetes and Chronic Kidney Disease in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

SAMUEL S. ENGEL, SHAILAJA SURYAWANSHI, ROBERT G. JOSSE, ERIC PETERSON, RURY R. HOLMAN, TECOS STUDY GROUP, *Kenilworth, NJ, Toronto, ON, Canada, Durham, NC, Oxford, United Kingdom*

TECOS, a randomized, double-blind, placebo-controlled trial that assessed the impact of sitagliptin on cardiovascular outcomes, provides an opportunity to examine comparative safety-related outcomes in patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD) defined as an eGFR <60 ml/min/1.73m^2.

TECOS included 3,324 CKD patients (1,667 sitagliptin, 1,657 placebo) with mean (SD) age 68.8 (7.9) years and diabetes duration 13.7 (9.0) years; 62% were male. Over ~2.8 median years' follow-up, sitagliptin-assigned patients, compared with placebo-assigned patients, had generally similar rates of diabetic eye disease, diabetic neuropathy, renal failure, malignancy, bone fracture and pancreatitis (Table). The incidence of hypoglycemia requiring assistance was 3.4% and 3.3% in the sitagliptin and placebo groups, respectively.

In TECOS, no specific safety concerns were identified with the use of sitagliptin in T2DM patients with CKD.

Table.

Proportions of CKD patients in TECOS with:	Sitagliptin N=1667	Placebo N=1657
Any diabetes complication	40.1%	42.1%
Diabetic eye disease	3.1%	3.1%
Diabetic neuropathy	3.9%	3.6%
Renal failure	3.3%	3.6%
Malignancy	4.3%	5.1%
Bone fracture	3.7%	3.3%
Pancreatitis	0.1%	0.1%

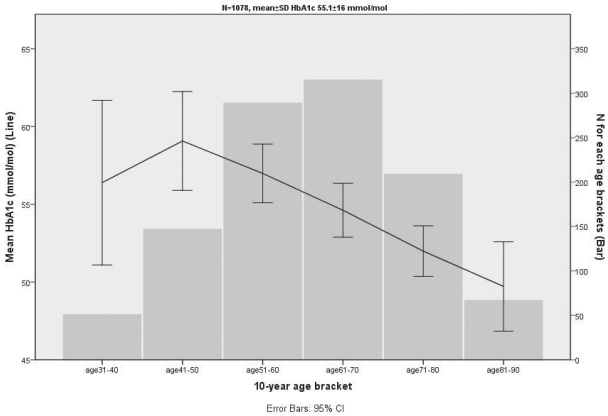
1182-P

Tighter Glycemic Control in Elderly Type 2 Diabetes Patients Attending an Irish Diabetes Clinic

SEONG KEAT CHEAH, CATHERINE DUANNE, ABIGAIL DURAK, SEAMUS SREENAN, JOHN MCDERMOTT, TOMMY KYAW TUN, *Dublin, Ireland*

Glycemic targets in the elderly should be carefully individualized due to possible co-morbidities in this age group. To compare glycemic control in elderly patients to younger age groups, we retrospectively reviewed HbA1c (A1c) measured in 1078 type 2 diabetes (T2DM) patients consecutively attending for annual diabetes review. The overall mean±SD A1c was 55.1±16 mmol/mol. Patients >65 y (N=462, mean±SD age 73.3±6 y, mean BMI 31.4±5.5 kg/m^2) had a lower mean A1c of 52.7±14.1 mmol/mol when compared with their counterparts aged <65 (N=616, mean±SD age=53.5±8 y, mean BMI 32.4±6.8 kg/m^2) who had a mean HbA1c of 56.9±17.0 mmol/mol, p<0.05 for comparison of A1c. Insulin use and number of oral hypoglycemic medications were similar in those < and > 65 y. Mean A1c in patients >40 y declined when compared in 10-year age brackets (p<0.05, Figure 1) and was 9.4 and 7.1 mmol/mol lower in patients aged 81-90 and 71-80 y respectively compared to those aged 41-50 (p<0.05). We conclude that these data may reflect overtreatment of T2DM in elderly and we may need to review treatment plans for these patients.

Figure 1. Mean HbA1c for Each 10-year Age-bracket.



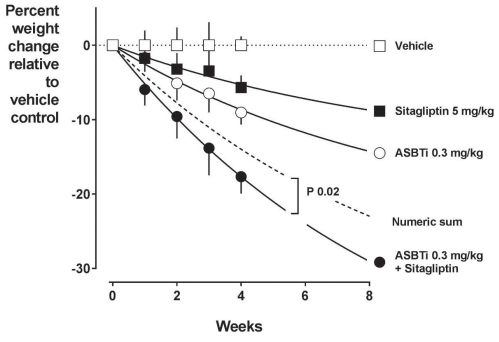
1183-P

Synergistic Effects of Inhibition of Bile Salt Transport and DPP-4 Activity in db/db Mice

BRONISLAVA GEDULIN, TED GREENE, SVETLANA NIKOULINA, ANDREW YOUNG, *San Diego, CA*

Bile salts are potent stimulators of secretion of GLP-1 and other peptides from enteroendocrine L-cells, found in distal portions of the gut. Apical bile salt transport inhibitors (ASBTi's), like Metformin, interrupt the absorption of bile salts at the terminal ileum and increase bile salt concentrations in the large bowel. The effects of stimulated GLP-1 secretion can be amplified by inhibition of DPP-4, its degrading enzyme. To assess the antidiabetic potential of ASBTi's (LUM002), and potential synergism with a DPP-4 inhibitor (sitagliptin), we orally dosed six groups of n=7, 8 *db/db* mice (age 7 w) with vehicle, sitagliptin 5mg/kg, LUM002 0.1mg/kg, LUM002 0.3mg/kg, sitagliptin+LUM002 0.1mg/kg, or sitagliptin+LUM002 0.3mg/kg daily. Body weight was measured weekly, HbA1c and fasting glucose after 4 weeks of treatment. The ΔΔ-HbA1c relative to week 0 and vehicle was -0.36, -0.32, -0.26 for sitagliptin and LUM002 0.1, 0.3mg/kg treatments respectively. The response to combined treatments (-0.78, -0.93) exceeded the sum of single treatments (0.68, 0.61). Mean fasting glucose (368, 267, 278 mg/dL; vehicle, sitagliptin, LUM002 0.3mg.kg) was normalized (129 mg/dL) with the combination. Weight loss with the combination was synergistic (see graph). In summary, an ASBTi combined with a DPP-4i exhibited synergistic effects on glycemic and weight loss endpoints in the *db/db* model of metabolic disease.

Figure.



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Moderated Poster Discussion ADA-Supported Research

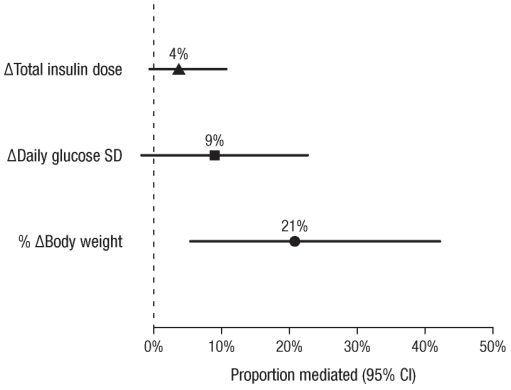
1184-P

Improved Treatment Satisfaction in People with Type 1 Diabetes Mellitus (T1DM) Treated with Canagliflozin (CANA)

ANNE L. PETERS, HELENA W. RODBARD, APRIL SLEE, SHANA TRAINA, *Los Angeles, CA, Rockville, MD, Seattle, WA, Raritan, NJ*

In a randomized Phase 2 study among people with T1DM as add-on to insulin, CANA, an SGLT2 inhibitor, provided reductions in A1c, insulin dose, and body weight vs. placebo (PBO) over 18 weeks. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to evaluate treatment satisfaction (n = 324). At week 18, subjects treated with CANA 100 and 300 mg reported greater improvements in treatment satisfaction vs. PBO (least squares mean changes in DTSQc total score of 12.1, 12.8, and 7.3, respectively). Subjects treated with CANA 100 and 300 mg reported less time experiencing hyperglycemia vs. PBO (62.2%, 70.6%, and 30.6% reported improvement, respectively). Product-method mediation analyses were used to evaluate the extent to which the effect of CANA treatment on DTSQc scores was mediated by insulin reduction, glycemic control, and percent change in body weight. Regression analyses suggest that reduction in total insulin dose and reduction in glycemic variability (measured by change in daily glucose standard deviation assessed using 9-point self-monitoring blood glucose) accounted for 4% and 9% of the relationship between CANA and satisfaction change, respectively (Figure). Change in body weight accounted for 21% of the relationship. These findings suggest that therapies that offer insulin reduction, reduced glycemic variability, and weight loss lead to increased treatment satisfaction.

Figure. Mediators of the Relationship between CANA Treatment* and Change in Overall Treatment Satisfaction Measured by the DTSQc at Week 18.



DTSQc, Diabetes Treatment Satisfaction Questionnaire change version; SD, standard deviation; CI, confidence interval.
*Mediation analysis was performed on the pooled CANA 100 and 300 mg groups.

Supported By: Janssen Global Services, LLC

1185-P

Effects of Dapagliflozin (DAPA), a Sodium Glucose Cotransporter 2 Inhibitor, on 24-Hour Glycemic Control in Patients with Type 2 Diabetes (T2D)

ROBERT R. HENRY, POUL STRANGE, RONG ZHOU, SERGEY B. ZHUPLATOV, TRACI MANSFIELD, DAVID KLEIN, ARIE KATZ, *San Diego, CA, Princeton Junction, NJ, Cincinnati, OH, Fort Washington, PA*

This 4-week (wk) randomized study compared the effects of DAPA 10 mg/d (N=50) vs. placebo (PBO; N=50) on 24-h glycemic control in adult patients with T2D on stable doses of Metformin (MET; ≥1500 mg/d) alone or insulin (INS; ≥30 U/d) ± up to 2 oral antidiabetes drugs. INS dose could be adjusted at the investigators discretion. Glucose concentration was measured over 7 days at lead-in and wk 4 using a continuous glucose monitoring (CGM) system (Dexcom®). The primary outcome was change from baseline (BL) to wk 4 in 24-h mean weighted glucose (MWG). Glucose fluctuation was quantified using CGM data by change from BL in the 24-h mean amplitude of glucose excursion (MAGE). Analyses were done for the overall population and by MET or INS strata. Treatment with DAPA significantly reduced 24-h MWG, 24-h MAGE, fasting plasma glucose and 2-h postprandial glucose compared with PBO. The proportion of time in euglycemia (blood glucose [BG] ≥70 and ≤180 mg/dL) was increased and time with BG >180 mg/dL was decreased with DAPA vs. PBO. There was a small increase in time with BG <70 with DAPA vs. PBO, driven by the DAPA + INS group, but no adverse events (AEs) of hypoglycemia were reported. The most common AE was urinary tract infections (6% in both arms). These data show that DAPA is effective in reducing both overall glycemia and 24-h glucose fluctuations in patients with T2D uncontrolled with MET or INS.

Table. Summary of Efficacy Results.

	Dapagliflozin 10 mg/d N=50	Placebo N=50
Primary Outcome		
24-hr MWG[a], mg/dL		
Baseline mean (SD)	177.9 (35.39)	182.6 (33.26)
Adjusted mean (SE) change baseline to day 28	–18.2 (4.33)	+5.8 (4.25)
Adjusted mean (SE) difference vs. placebo	–24.0 (6.08)	
p-value for treatment difference	<0.001	
Key Secondary Outcomes		
MAGE[a], mg/dL		
Baseline mean (SD)	102.7 (30.96)	108.6 (29.89)
Adjusted mean (SE) change baseline to day 28	–10.0 (4.14)	+5.3 (4.06)
Adjusted mean (SE) difference vs. placebo	–15.3 (5.80)	
p-value for treatment difference	0.01	
Fasting Plasma Glucose (FPG)[b], mg/dL		
Baseline mean (SE)	163.6 (9.82)	170.3 (8.06)
Adjusted mean (SE) change baseline to day 28	–26.2 (5.99)	+3.6 (5.98)
Adjusted mean (SE) difference vs. placebo	–29.7 (8.47)	
p-value for treatment difference	<0.001	
2-h postprandial glucose (PPG)[b], mg/dL		
Baseline mean (SE)	223.3 (8.25)	231.5 (6.57)
Adjusted mean (SE) change baseline to day 28	–49.5 (6.61)	–13.2 (6.46)
Adjusted mean (SE) difference vs. placebo	–36.3 (9.25)	
p-value for treatment difference	<0.001	
Percent of time with blood glucose >180 mg/dL[c], %		
Baseline mean (SD)	40.9 (24.29)	44.1 (22.42)
Adjusted mean (SE) change baseline to day 28	–12.6 (2.65)	+3.5 (2.60)
Adjusted mean (SE) difference vs. placebo	–16.1 (3.72)	
p-value for treatment difference	<0.001	
Percent of time with blood glucose ≥70 and ≤180 mg/dL[c], %		
Baseline mean (SD)	58.4 (24.08)	55.0 (22.22)
Adjusted mean (SE) change baseline to day 28	+12.2 (2.60)	–2.8 (2.55)
Adjusted mean (SE) difference vs. placebo	+15.0 (3.65)	
p-value for treatment difference	<0.001	
Percent of time with blood glucose <70 mg/dL[c], %		
Baseline mean (SD)	0.8 (1.70)	1.0 (1.98)
Adjusted mean (SE) change baseline to day 28	+0.3 (0.30)	–0.6 (0.29)
Adjusted mean (SE) difference vs. placebo	+1.0 (0.42)	
p-value for treatment difference	0.023	

[a]24-hr MWG and MAGE were calculated from CGM data. Analysis was based on the intent-to-treat population using an analysis of covariance model (ANCOVA) with change in 24-hour MWG as the dependent variable, DAPA treatment and MET/INS use as factors and baseline 24-hour MWG as a covariate; [b]FPG was analyzed from blood samples drawn at randomization (day 1) and on day 28 (LOCF), and 2-h PPG was analyzed from blood samples on Day -13 and Day 22 using a similar ANCOVA model as the one described for MWG; [c]Percent of time with blood glucose >180 mg/dL (hyperglycemic range), ≥70 and ≤180 mg/dL (euglycemic range and < 70 mg/dL (hypoglycemic range) was calculated from CGM data.

1186-P

Distinct Glucose Lowering Properties of Ipragliflozin Depending on Body Weight Change

EIJI KUTOH, ASUKA WADA, MITSURU HIRATE, *Tokyo, Japan, Gyoda, Japan*

The aim of this study is to investigate the link between the changes of body weight and those of diabetic parameters in drug naïve subjects with T2DM treated with ipragliflozin. The subjects were administered only 25-50 mg ipragliflozin (n=28). At 3 moths, levels of diabetic parameters were compared with those at baseline. Significant decreases of HbA1c (10.06 to 8.18%, p<0.00001) and BMI (-2.4%, p<0.005) were observed. However, no correlations were noted between the changes (Δ) of these parameters. Then, the subjects were divided into two groups; those who significantly lost weight (ΔBMI≤-0.75; termed "group L(ost)," p<0.00001, n=16) and others who did not lose weight (ΔBMI> -0.75; termed "group N(eutral)," n.s., n=12). In these two groups, similar reductions of HbA1c were observed (group L: 10.08% to 8.15%, p<0.0001;

group N: 9.97% to 8.55%, p<0.00001). HOMA-R significantly reduced only in group L (-22.7%, p<0.05), while HOMA-B increased in both groups with significant inter-group differences (p<0.05; +74.4% in group N vs. +48.6% in group L). In group L, significant correlations were observed between ΔHbA1c and ΔHOMA-R (R=0.547, p<0.03), while in group N, significant negative correlations were observed between ΔHbA1c and ΔHOMA-B (R=-0.493, p<0.05). Insignificant increases of free fatty acids (FFA, +9.5%, n.s.) were noted in group L, while significant reductions of FFA (-22.5%. p<0.03) were observed in group N. Significant negative correlations between ΔFFA and ΔHOMA-B (R=-0.651, p<0.02), and positive correlations between ΔFFA and ΔHbA1c (R=0.435, p<0.05) were noted in group N. Taken together, these results suggest that 1.) body weight reduction with ipragliflozin is not associated with its glycemic efficacy. 2.) glycemic efficacy of ipraglizlozin is mediated by two distinct pathways; decreasing insulin resistance is dominant in those who lose weight and activating beta-cell function through decreasing FFA (lipotoxicity) is dominant in others who do not lose weight.

1187-P

Safety and Pharmacokinetics of DS-8500a, a Novel GPR119 Agonist, after Multiple Oral Doses in Healthy Japanese Males

MANABU KATO, HIDETOSHI FURUIE, FUJIKO TSURUTA, *Tokyo, Japan, Osaka, Japan*

DS-8500a is a novel agonist of the G-protein coupled receptor (GPR119), which is expressed in pancreatic beta cells and intestinal L cells in humans. It is being developed for the treatment of type 2 diabetes mellitus. Results from a single-ascending dose study showed that DS-8500a was well tolerated at a dose range of 1 mg to 600 mg (capsule formulation). The objective of this study was to evaluate safety, tolerability and pharmacokinetics of multiple oral doses of DS-8500a for 7 days in healthy Japanese adult males. This was a single-center, randomized, double-blind, placebo-controlled, multiple-oral-dose study. DS-8500a tablets at doses of 50 mg, 100 mg, or a matching placebo were administered orally once daily after breakfast for 7 days. Twelve subjects were randomized at a ratio of 9:3 to receive DS-8500a or placebo in each dose level cohort. Pharmacokinetic parameters were calculated using a non-compartmental method. Safety assessments included adverse events, vital signs, standard 12-lead electrocardiography (ECG), and laboratory tests. Cmax and AUCtau of DS-8500a at 100 mg dose on Day 7 (1310 ng/mL and 13200 ng·h/mL) increased in a less than dose-proportional manner compared with those at 50 mg dose (812 ng/mL and 7910 ng·h/mL). DS-8500a Tmax at 50 mg and 100 mg occurred at 2.5 and 4.5 hr with a half-life of 12.2 and 12.9 hr, respectively. Plasma DS-8500a concentration reached a steady state by Day 7. No deaths or other serious adverse events were reported. All adverse events were mild in severity and occurred in 1 of the 9 subjects in the 50-mg group, 2 of the 9 subjects in the 100-mg group, and 1 of the 6 subjects in the placebo group. No notable changes were found in vital signs, standard 12-lead ECG or laboratory values (including hypoglycemia). Repeated doses of DS-8500 50 mg and 100 mg for 7 days were safe and well tolerated in healthy Japanese males. The pharmacokinetics profile of DS-8500 is compatible with once daily dosing.

1188-P

Combined Treatment with Metformin and Pioglitazone of Bladder Epithelial Cells Induces Cell Cycle Progression and Activation of Oncogenic Signaling Pathway in High Glucose with Insulin Condition

DAEJIN KIM, BYUL-NIM AHN, GA BIN PARK, YEONG SEOK KIM, DAE YOUNG HUR, JAE WOOK YANG, MIN JEONG KWON, JEONG HYUN PARK, SOON HEE LEE, *Busan, Republic of Korea*

Type 2 diabetes is significantly associated with the increase the risk of cancers. Metformin and synthetic *peroxisome proliferator-activated receptor gamma (*PPARγ) ligand, thiazolidinedione (TZD) have anti-proliferative activity against cancer. In contrary, there is concern that long-term usage of TZDs increases the risk of bladder cancer. Meanwhile, little is known about the molecular mechanisms and precise environments by which PPARγ agonists with high glucose and insulin have an influence on carcinogenesis in bladder epithelium. Metformin or pioglitazone suppressed the cell viability in dose- and time- dependent manner, whereas high glucose or high glucose with insulin restored the proliferation rate and enhanced the viability of T24 cell and human primary bladder epithelial cell (HBlEpC) treated with single drug or combination. Prolonged exposure to high glucose and high insulin supplementation of T24 cell and HBlEpC not only enhanced the expression of cyclin D-Cdk4 and cyclin E-Cdk2 but also attenuated the activation of Cdk inhibitors, p21 and p15/16. The levels of tumor suppressor proteins, including p53 and caveolin-1 (cav-1) were suppressed in drug-treated HBlEpC; however, the expression of oncogenic protein, c-myc, was increased. Furthermore, the mRNA of Bax is significantly down-regulated in drug-treated T24 cells and HBlEpC cultured in the presence of high glucose or high glucose with insulin. The activation of ERK and p38 MAPK were also detected in T24 cell and HBlEpC co-treated with Metformin and pioglitazone in the condition of high glucose with insulin. Taken together, our study suggest that stimulation with antidiabetic drug has a potential effect on carcinogenesis of bladder epithelium under hyperglycemic and hyperinsulinemic condition.

1189-P

Safety and Efficacy of BI 187004, a Selective 11beta-Hydroxysteroid Dehydrogenase 1 (11b-HSD1) Inhibitor, after 4 Weeks of Treatment in Patients with Type 2 Diabetes

SUSANNA FREUDE, TIM HEISE, MATIAS NORDABY, BARBARA PEIL, CORDULA ZELLER, MICHAEL WOLFF, JOHN P. SABO, LAURENT VERNILLET, HANS-JUERGEN WOERLE, ULRIKE GRAEFE-MODY, *Ingelheim, Germany, Neuss, Germany, Biberach, Germany, Ridgefield, CT*

The 11b-HSD1 inhibitor BI 187004 is a clinical development candidate for the treatment of type 2 diabetes mellitus (T2DM). We characterized safety, tolerability, pharmacokinetic, and pharmacodynamic effects on glucose and other metabolic parameters of BI 187004 in overweight/obese patients with T2DM. Patients received placebo or BI 187004 (20, 80, 240 mg) once daily for 28 days either as monotherapy (arm 1) or on top of a stable Metformin background therapy (240 mg or placebo, arm 2) in a randomized, double-blind (within dose groups) fashion. A total of 103 patients entered the study (15-16 per dose group in arm 1; 20-21 per dose group in arm 2). Plasma exposure of BI 187004 increased more than proportionally with dose. Pharmacodynamic assessment demonstrated an effect of BI 187004 on 11b-HSD1 inhibition: the ratio of urinary metabolites tetrahydrocortisol and tetrahydrocortisone decreased by ~75% at steady state across all BI 187004 doses, concentrations of adrenocorticotropic hormone (ACTH) increased and plasma cortisone decreased slightly but both stayed within normal range. Despite this evidence of 11b-HSD1 inhibition, BI 187004 did not improve fasting plasma glucose or weighted mean glucose after 28 days of treatment as compared to baseline and placebo in either arm. Also, there was no relevant improvement of blood pressure, body weight, or LDL cholesterol. The incidence of treatment related adverse events was comparable between placebo (19-33%) and BI 187004 (up to 31%), and there were no clinically relevant deviations in clinical laboratory, vital signs, and ECG. In conclusion, BI 187004 was well tolerated in T2DM patients and inhibited 11b-HSD1. However, this compound did not improve glycemic control or other metabolic parameters after 4 weeks of treatment. These results do not suggest a therapeutic potential for BI 187004 in T2DM.

Supported By: Boehringer Ingelheim

1190-P

Glucose-Lowering and Cardiovascular Medication Use Outside Western Europe and North America from 2006-2012

STEPHANIE K. TANAMAS, SILVER K. BAHENDEKA, CHERN-EN CHIANG, JUAN JOSE GAGLIARDINO, SANJAY KALRA, ANDREA LUK, HIROSHI MAEGAWA, AYESHA A. MOTALA, RAMACHANDRAN AMBADY, KHALED A. TAYEB, OLGA VIKULOVA, JENCIA WONG, FILIP SURMONT, JONATHAN E. SHAW, *Phoenix, AZ, Kampala, Uganda, Taipei, Taiwan, La Plata, Argentina, Karnal, India, Hong Kong, China, Shiga, Japan, Durban, South Africa, Chennai, India, Mecca, Saudi Arabia, Moscow, Russian Federation, Sydney, Australia, Shanghai, China, Melbourne, Australia*

The aim of this study was to characterize the use of glucose-lowering (GLM) and cardiovascular medication in people with type 2 diabetes in countries outside Western Europe and North America between 2006 and 2012. Ten clinical services (from Argentina, Australia, Hong Kong, India, Japan, Saudi Arabia, South Africa, Uganda) and 2 national registers (Russia, Taiwan) (n of patients per site: 278 - 1737000) which use electronic medical records to manage people with diabetes were identified. With regard to GLM, between 2006 and 2012, the percentage of patients on monotherapy or non-pharmacological therapy fell in all sites (range -15 to -39%) except for one (+12%). The percentage of patients on monotherapy with sulphonylureas (SU) decreased in all sites (range -84 to -4%), while change in monotherapy with Metformin varied between -41 to +206%. Total SU use decreased little with only 3 sites demonstrating a decrease ≥20%. Mean HbA1c decreased (range -2 to -7%) or remained stable in six sites and increased in four sites (range 5 to 10%). Statin use increased in all sites (range 19 to 139%) and mean serum LDL cholesterol decreased minimally (range -0.003 to -0.3 mmol/l). Use of angiotensin-receptor blockers increased in all sites (range 16 to 143%) while use of angiotensin-converting enzyme inhibitors decreased in all sites (range -51 to -9%) except for two sites (+12 and +4167%). Antihypertensive therapy use increased (range 3 to 27%) except in two sites (-24 and -3%), but no consistent change in systolic blood pressure was observed (range -3 to +6%). Despite marked differences in healthcare settings, there were consistent medication patterns. There was an

For author disclosure information, see page A696.

increased intensity of GLM, continued use of SUs, and increased use of antihypertensives and statins. Despite increased therapy, improvements in HbA1c, blood pressure and LDL were absent or only very modest.

Supported By: AstraZeneca

1191-P

Gemigliptin, a Dipeptidyl Peptidase-4 Inhibitor, Suppresses Laser-induced Choroidal Neovascularization in a Rat Model

EUNSOO JUNG, SUNG-HO KIM, JUNGHYUN KIM, *Seoul, Republic of Korea, Daejeon, Republic of Korea*

Choroidal neovascularization (CNV) is a characteristic feature of age-related macular degeneration (AMD). The neovascular AMD is currently treated by several anti-vascular endothelial growth factor (VEGF) agents. However, intravitreal injection of these agents can be associated with adverse events, and there are non-responders and suboptimal responders to anti-VEGF treatment. Therefore, several drug candidates for CNV that target molecules other than VEGF are under study for possible clinical usage. Gemigliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is an oral agent for type 2 diabetes, but its effects on wet AMD have not yet been reported. In this study, we evaluated the effect of gemigliptin on laser-induced CNV in a rat model. Experimental CNV was induced by laser photocoagulation in Brown Norway rats. Gemigliptin (5 or 10 mg/kg/day) was administered orally once per day for ten days after laser photocoagulation. Choroidal flat mounts were prepared to measure CNV areas. We used a protein array to evaluate the expression levels of angiogenic factors. The CNV area in gemigliptin-treated rats were significantly lower than in vehicle-treated rats. Gemigliptin decreased the expression levels of MCP-1, PAI-1, and VEGF. Additionally, gemigliptin also inhibited macrophage infiltration in CNV areas. These results suggest that gemigliptin exerts anti-angiogenic effects on laser-induced CNV by inhibiting the expression of MCP-1, PAI-1 and VEGF.

1192-P

DS-8500a, a Novel GPR119 Agonist Preserves Pancreatic β-cell Function and Prevents Glycohemoglobin Increase Compared with Sitagliptin in Type 2 Diabetic Mice

TOMOMI YOSHITOMI, KOJI MATSUMOTO, NAOMI TANAKA, KANAKO TAKAHASHI, *Tokyo, Japan*

DS-8500a, a novel GPR119 agonist, is expected to enhance glucose-stimulated insulin secretion, promote GLP-1 secretion, and exert antidiabetic effects. The objective of this study was to evaluate long-term antidiabetic effects of DS-8500a compared with sitagliptin in rodent models of T2DM (db/db and NONcNZO10/LtJ mice). In db/db mice, treatment with DS-8500a (30 mg/kg, po) from 5 to 10 weeks of age improved first-phase insulin secretion after an in IV glucose administration, whereas a defect in insulin secretion was observed with both vehicle and sitagliptin (30 mg/kg). Under food restriction (fed 6 to 8 hours per day) over 10 weeks, glycohemoglobin (GHb) increased gradually in vehicle (3.12±0.08 and 6.54±0.22% at 5 and 15 weeks of age, respectively). Sitagliptin did not prevent GHb increase, while DS-8500a significantly prevented it GHb increase (5.92±0.23%, $P<0.05$ vs. vehicle). In NONcNZO10/LtJ mice, which develop maturity-onset diabetes, a single dose sitagliptin (30 mg/kg, po) lowered glucose AUC after an oral glucose administration ($P<0.05$ vs. vehicle), while DS-8500a (30 mg/kg) did not show a significant effect on the AUC. However, 3 weeks treatment (20 to 23 weeks of age) with DS-8500a (12 and 36 mg/kg, food admixture) prevented GHb increase ($P<0.05$ vs. vehicle, respectively), whereas sitagliptin (36 mg/kg) did not. The preventative effect of DS-8500a on GHb increase lasted for 9 weeks (20 to 29 weeks of age, ΔGHb: 1.8±0.4 vs. 0.4±0.4, $P<0.05$ for vehicle and DS-8500a, respectively). After 10 weeks treatment, histopathological analysis revealed that DS-8500a preserved morphology of pancreatic islets better than vehicle and sitagliptin. In conclusion, these results suggest that DS-8500a improves β-cell function and GHb increase in animal models of T2DM suggesting it could represent a novel class of glucose-lowering agent with a potential for long-term antidiabetic effects in patients with T2DM.

1193-P

Examination for the Alterations of Serum and Urinary Sodium Levels after Treatment with SGLT2 Inhibitors in Type 2 Diabetes

TATSUO ISHIZUKA, MOTOCHIKA ASANO, KEI FUJIOKA, YOSHIHIKO KITADA, DAIKI ANDOH, TAKAKO MARUYAMA, KOUJI YAMADA, *Gifu, Japan*

We have examined the effect of SGLT2 inhibitors (SGLT2i) on serum (Na) and urinary sodium levels (UNa) in 12 patients (6 men and 6 women, age 66.3 ± 9.7) with type 2 diabetes to clarify the interrelationship between UNa and blood pressure (BP). We used five kinds of SGLT2i (tofoglyflozin in 7 cases, luceoglyflozin 2 cases, dapaglyflozin, canagliflozin and ipraglyflozin in each 1 case). Before treatment with SGLT2i, fasting plasma glucose (FPG), HbA1c, body weight and serum sodium levels were 145 ± 22 mg/dl, 7.8 ±3.5%, 63.8 ±13.1 kg and 140 ± 4 mEq/l, respectively. After treatment with SGLT2i FPG HbA1c, body weight and systolic blood pressure were significantly decreased ($P < 0.05$-0.01). However, no changes of Na and increasing hematocrit levels ($P < 0.05$) were observed. These results suggest that SGLT2i may stimulate urinary sodium excretion. UNa (mEq/g.creatinine) calculated by measuring casual urinary sodium and creatinine levels were able to be measured in 5 patients with type 2 diabetes exactly before and after for 1-6 months treatment with SGLT2 inhibitors. UNa were measured in 12 patients with type 2 diabetes without using diuretics, but failed to measure urinary sodium excretion before treatment with SGLT2 inhibitors in 5 patients. Urinary sodium excretion levels after treatment with SGLT2 inhibitors for 6 months (259.8 ± 143.6 mEq/g.cretinine) were significantly increased ($P < 0.02$) compared with before treatment with SGLT2 inhibitors (73.0 ± 15.7 mEq/g.creatinine). Increasing in UNa in five patients with type 2 diabetes before and after treatment with SGLT2i for 1 month was significantly observed ($P < 0.05$) and increased sodium excretion had been maintained for 6 months. Finally, SGLT2 inhibitors apparently improve not only diabetic control but also circulatory system via increasing in urinary sodium excretion.

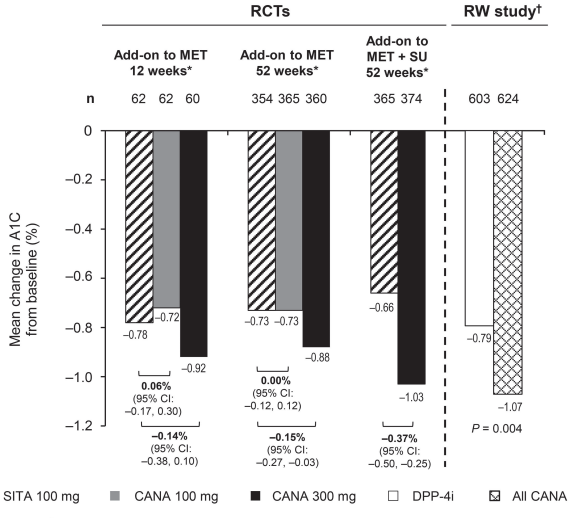
1194-P

Efficacy of Canagliflozin (CANA) vs. Dipeptidyl Peptidase-4 Inhibitors (DPP-4i) in Patients with Type 2 Diabetes Mellitus (T2DM): Results from Randomized, Controlled Trials (RCTs) and a Real-World (RW) Study

WILLIAM CANOVATCHEL, SARAH THAYER, WING CHOW, RONG QIU, MICHAEL J. DAVIES, *Raritan, NJ, Eden Prairie, MN*

In RCTs, CANA was shown to be more effective than the DPP-4i sitagliptin (SITA) in lowering glucose. RCT and RW results tend to differ as RW studies may include a broader set of patients with more advanced conditions; thus it is important to assess the effects of agents in clinical practice. We compared the A1c-lowering efficacy of CANA 100 and 300 mg vs. SITA 100 mg in 3 RCTs of patients with T2DM, and the effectiveness of CANA (pooled data for all doses) in a retrospective RW matched control-cohort study using U.S. integrated claims and laboratory data from a large population of insured patients with T2DM (65% and 34% of patients received CANA 100 or 300 mg, respectively [1% other]). Patients in the CANA cohort were matched 1:1 to patients in the DPP-4i cohort using propensity score matching that incorporated demographics and baseline characteristics. In RCTs with baseline A1c ~8.0%, CANA 100 mg provided similar and CANA 300 mg provided greater A1c reductions vs. SITA 100 mg (Figure). In the RW study with baseline A1c ~9.0%, greater A1c reductions were seen with CANA (-1.07%) vs. DPP-4i (-0.79%). In summary, the relative magnitude of A1c reduction with CANA and SITA was similar in the RCT and RW studies; CANA consistently lowered A1c vs. DPP-4i in patients with T2DM.

Figure. Change from Baseline in A1c: RCTs vs. RW Study.



*Data are least squares mean.
†Mean (median) follow-up of 182.3 (191.0) days for DPP-4i and 184.2 (197.0) days for CANA.

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1195-P

Euglycemic DKA Post-Gastric Bypass in a DM2 Patient on a SGLT2 Inhibitor: Lessons Learned, New Recommendations

MAEVE C. DURKAN, EOIN P. O'SULLIVAN, COLM O'BOYLE, *Cork, Ireland*

A 51 year old woman, with a 10 year history of DM2 is referred 2 days post gastric bypass surgery for evaluation with fever, nausea, abdominal pain, tachypnoea. Her DM regime included dapagliflozin 10mgs, Metformin 1gm BD and Novomix 120 units BD. She had CKD stage 3a and a stable baseline eGFR of 50. Pre-op HbA1c was 71 mmol/l. As per the 2 week pre-surgery protocol, she was put on a high protein, low carbohydrate diet. All medications and insulin therapies were continued with recommendation for insulin adjustment commensurate with glucose readings. Her surgery was uneventful. DM medications and insulin were held post-op with protocol to restart if sugars rose > 10 mmol/l. She spiked a temperature 48 hours postop, O2 sats fell to 94%, CRP rose to 200mg/l and CT confirmed a left lobar pneumonia. Her anastomotic site was intact. Her GFR remained stable. ABGs confirmed a PH 7.164, bicarb 7.3, PO2 15, 5 kPa, PCo2 2.7 kPa, lactate 1 mml/l and anion gap of 19.8 mEq/l, all confirming metabolic anion gap acidosis. Her FBS day 1 post op was 8.7 mmol/l, and on day 2 was 13 (serum osmolality 331 mOsm/l). Glucose monitoring in that 48 hours confirmed values < 10. A diagnosis of eugylcaemic ketoacidosis was made, multifactorial in aetiology BUT felt predominantly attributable to concomitant SGLT2 therapy (although on hold). She was commenced on IV insulin, requiring 240 units/day, taking 5 days before metabolic milieu normalized. She was converted to Glargine 20 units, glucophage was recommended and glucose remained normal. Anti GAD antibodies were confirmed negative. C-peptide measured (pre next lantus dose) 1.12 ug/l (0.8-5.2). In summary, the high protein, low carbohydrate diet may have accelerated a ketogenic state, aggravated by SGLT2 therapy and attendant hyperglucagonaemia prompting a risk for ketosis that was exaggerated in the post operative fasting state and concomitant infection. Our pre-operative protocol has now changed to specifically EXCLUDE SGLT2 therapy in the 2 week high protein diet pre-op phase.

1196-P

Safety and Effectiveness of PBI-4050 in Type 2 Diabetic Subjects with Metabolic Syndrome: Results of an Open-Label Pilot Study

PETER A. SENIOR, LAURIE MEREU, JEFF WINTERSTEIN, ALINE HAGERIMANA, PIERRE LAURIN, JOHN MORAN, *Edmonton, AB, Canada, Laval, QC, Canada*

Despite recent advances, better treatments for type 2 diabetes (T2DM) complicated by the metabolic syndrome (MS) are desirable. PBI-4050 is a novel first-in-class orally active compound which in pre-clinical studies has demonstrated anti-fibrotic activity in multiple organs, including in the pancreas, and to improve glucose tolerance in rodent models of T2DM. We conducted an open label, single arm Phase 2 study of oral administration of PBI-4050 800 mg once daily for 12 weeks in T2DM subjects with MS with suboptimal control despite oral antihyperglycemic medications. We report on the first 11 subjects that have completed 12 weeks treatment (6 male, 5 female, age 60 ± 11 years, BMI 34.3 ± 5.0 kg/m^2, waist circumference 112 ± 14 cm, HDL 1.33 ± 0.3 mmol/L, triglycerides 1.62 ± 0.7 mmol/L). After 12 weeks, 10 out of 11 patients experienced an improvement in their HbA1c values, with an overall mean reduction of 0.6% (7.9 ± 1.0 vs. 7.3 ± 1.0%; p = 0.0302). In the 6 subjects with HbA1c > 7.5% at entry the HbA1c reduction averaged -1.0%. The subjects did not gain weight during the 12 week treatment: the mean weight change was -0.28 kg (p = 0.5095) Only one episode of asymptomatic hypoglycemia (3.9 mmol) was observed after over 200 weeks of exposure when PBI-4050 was added to conventional antihyperglycemic medications. No subject experienced a treatment related severe adverse event. PBI4050 is safe and well tolerated in T2DM subjects with MS and is effective in improving glycemic control. The efficacy of PBI-4050 will be tested in a double-masked, placebo-controlled RCT. (NCT02562573).

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1197-P

Imeglimin Improves Insulin Sensitivity in an Adult STZ Rat Model

SOPHIE HALLAKOU-BOZEC, SEBASTIEN BOLZE, MICHELINE KERGOAT, MICHAEL RODEN, HAROLD E. LEBOVITZ, *Lyon, France, Chilly Mazarin, France, Düsseldorf, Germany, New York, NY*

Imeglimin is a novel glucose-lowering agent improving insulin secretion and sensitivity. Imeglimin beneficial effect on insulin sensitivity was first evidenced during an insulin tolerance test in a high fat high sucrose diet mouse model and further through an improvement in Stumvoll and Matsuda sensitivity indexes during an OGTT in type 2 diabetic patients. This study describes Imeglimin effect on insulin sensitivity in a euglycemic hyperinsulinemic clamp in STZ rat. 10 days post STZ injection (50 mg/kg ip), 12 week-old diabetic rats were treated with Imeglimin (150 mg/kg bid orally) during 15 days. After both acute and 10 days Imeglimin administration, oral glucose tolerance in overnight fasted STZ rats was strongly improved (iAUC glucose: -41% and -35% p<0.001 respectively). Hepatic glucose production (GPR) and utilization (GUR) rates were evaluated both in the basal state and during euglycemic hyperinsulinemic clamp (insulin: 0.5 U/h/kg), performed in overnight fasted STZ rats after 15 days of Imeglimin treatment. No significant changes of GPR and GUR were observed in the basal state. During the clamp, at similar level of euglycemia and hyperinsulinemia, steady state glucose infusion rate was strongly and significantly increased in STZ rats after Imeglimin treatment compared to controls (+209%, p<0.01). Imeglimin treatment significantly decreased hepatic GPR (-40%, p<0.05). GUR tended to increase though not significantly in Imeglimin-treated group (+23%, p<0.06). Imeglimin induced a potent beneficial effect on glucose tolerance after both acute and chronic treatment in overnight fasted adult STZ rats. In this model of deep insulinopenia, Imeglimin clearly improved hepatic insulin sensitivity during the euglycemic hyperinsulinemic clamp. As Imeglimin was previously shown to increase glucose stimulated insulin secretion in various models including T2DM patients, this work confirms Imeglimin effects on insulin sensitivity and its uniqueness in targeting both insulin secretion and insulin action.

1198-P

Effect of Empagliflozin on Nephropathy in Subgroups by Age: Results from EMPA-REG Outcome

RICHARD M. BERGENSTAL, PAOLO CALABRO, MARIO MALDONADO LUTOMIRSKY, MAXIMILLIAN VON EYNATTEN, MICHAELA MATTHEUS, JOHN LACHIN, CHRISTOPH WANNER, *Minneapolis, MN, Naples, Italy, Ingelheim, Germany, Rockville, MD, Würzburg, Germany*

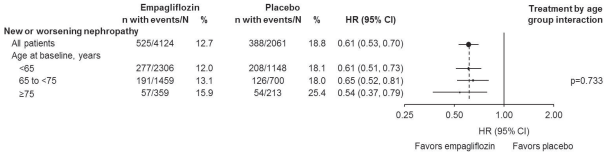
In the EMPA-REG Outcome trial, empagliflozin (EMPA) given in addition to standard of care significantly reduced the risk of new or worsening nephropathy vs. placebo (PBO) in patients with type 2 diabetes (T2DM) and high CV risk. We investigated the effect of age on the reduction in new or worsening nephropathy with EMPA.

Patients in EMPA-REG Outcome were randomized to receive EMPA 10 mg, EMPA 25 mg, or PBO. New or worsening nephropathy (defined as new onset of macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease) was analyzed in the pooled EMPA group vs. PBO in subgroups by baseline age (<65, 65 to <75, ≥75 years).

A total of 7020 patients were treated. Median observation time was 3.1 years. At baseline, mean (SD) age was 63.1 (8.6) years and 63.2 (8.8) years in the EMPA and PBO groups, respectively, and mean (SD) HbA1c was 8.07 (0.85)% and 8.08 (0.84)% in the EMPA and PBO groups, respectively. The benefit of EMPA vs. PBO on new or worsening nephropathy was consistent across age categories (Figure). Across age subgroups, reported adverse events were consistent with the known safety profile of EMPA.

EMPA, in addition to standard of care, reduced the risk of new or worsening nephropathy in patients with T2DM and high CV risk irrespective of age.

Figure. Cox Regression Model Including Sex, Baseline Body Mass Index, Baseline HbA1c, Baseline Estimated Glomerular Filtration Rate, Region, Treatment, Age Group and Treatment by Age Group Interaction, in Patients Treated with ≥1 Dose of Study Drug.



Supported By: Boehringer Ingelheim and Eli Lilly and Company

1199-P

Efficacy and Safety of Gemigliptin in Type 2 Diabetes Patients with Moderate to Severe Renal Impairment

SUN AE YOON, BYOUNG GEUN HAN, SUNG GYUN KIM, SANG YOUB HAN, YOUNG-IL JO, KYUNG HWAN JEONG, KOOK-HWAN OH, HYOUNGCHUN PARK, SUN-HEE PARK, SHIN-WOOK KANG, KI-RYANG NA, SUN WOO KANG, NAM-HO KIM, SUNG-HO KIM, YOUNGHWAN JANG, DAE RYONG CHA, GUARD STUDY, *Uijeongbu, Republic of Korea, Wonju, Republic of Korea, Anyang, Republic of Korea, Goyang, Republic of Korea, Seoul, Republic of Korea, Daegu, Republic of Korea, Daejeon, Republic of Korea, Busan, Republic of Korea, Gwangju, Republic of Korea, Ansan, Republic of Korea*

Renal impairment in type 2 diabetes mellitus (T2DM) limits the available glucose-lowering medication and requires frequent monitoring of renal

For author disclosure information, see page A696.

function. Gemigliptin has balanced elimination between urinary/fecal excretion and hepatic metabolism. Thus, it needs no dose adjustment in patient with moderate to severe renal impairment. This study evaluated the efficacy and safety of gemigliptin in type 2 diabetic patients with moderate to severe renal impairment. This randomized, double blind, parallel group Phase 3b study comprised a 12-week, placebo-controlled phase followed by a 40-week, double blind active-controlled extension phase. Patients (mean HbA1c 8.4%; age 62.0 years; BMI 26.2 kg/m^2, duration of T2DM 16.3 years; eGFR 33.3 mL/min/1.73 m^2) treated with gemigliptin (n=66) or placebo (n=66) for 12 weeks, then placebo group was switched to linagliptin 5 mg q.d and treatment continued to week 52. Primary endpoint was HbA1c change from baseline at week 12. At week 12, adjusted mean ± SE change HbA1c with gemigliptin was -0.83 ± 0.14% (change with placebo 0.38 ± 0.14%; difference -1.21, 95% CI -1.54 to -0.89; p<0.0001). After 52 weeks, adjusted mean ± SE change from baseline in HbA1c was -1.00 ± 0.21% and -0.65 ± 0.22% in the gemigliptin and linagliptin, respectively. Urinary albumin creatinine ratio (UACR) at week 52 was reduced by 28.0% (95% CI -40.2 to -13.3) with gemigliptin compared with 4.3% (95% CI -19.7 to 14.2) with linagliptin, with a between-group difference of 24.8% (95% CI -41.8 to -2.9; p=0.0294). During the 40-week extension, adverse events (AEs) were reported in 68.0% and 73.1% of subjects on gemigliptin and linagliptin, respectively. The incidence of hypoglycemia was similar among treatment groups (gemigliptin, 20.0%; linagliptin, 28.8%). There was no meaningful change from baseline in body weight (gemigliptin, 0.28 kg; linagliptin 0.33 kg). In conclusion, gemigliptin was efficacious and well tolerated in T2DM patients with moderate to severe renal impairment.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF COMPLICATIONS

1200-P

A Diabetic Ketoacidosis (DKA) Power Plan to Reduce Frequency of Rebound Hyperglycemia

POOJA MANROA, ELENA MORARIU, ROSEANN J. SALATA, AMY C. DONIHI, JODIE A. REIDER, RONALD CODARIO, RUNA ACHARYA, MARY T. KORYTKOWSKI, *Pittsburgh, PA*

DKA management following acute volume resuscitation and transition to subcutaneous (SC) insulin is inconsistent. Untimely discontinuation of Intravenous (IV) Insulin and insufficient dosing of SC insulin increase risk for rebound hyperglycemia and recurrent DKA. To overcome these deficiencies, an established DKA protocol was revised and implemented as a DKA Powerplan (PP) to guide continued IV insulin and transition to SC insulin. PP efficacy was investigated by comparing the following outcomes during similar time periods pre and post implementation: appropriateness of IV insulin discontinuation; recurrent DKA; rebound hyperglycemia (blood glucose (BG) > 300 mg/dl); and hypoglycemia (BG < 70 mg/dl) in the 24 hours following IV insulin discontinuation. Discontinuation of IV insulin was defined as appropriate if performed when BG < 200 mg/dl with a normal anion gap (AG). Recurrent DKA was defined as new increase in AG. Retrospective chart review was performed for patients admitted with primary diagnosis of DKA between August and September of the year preceding (pre-PP, n=25) and following (post-PP, n=25) DKA PP implementation. The groups were similar in age (pre- vs. post-PP: 40±12 vs. 35±15 yrs), BMI (26.5±6.4 vs. 25.5±5.4 kg/m^2), gender (males 44 vs. 40%), HbA1c (11.7±2.2 vs. 11.3±2.9%), admission BG (547±212 vs. 591±227 mg/dl) AG (26±7 vs. 28±7), or time to AG closure (8±4 vs. 7.5±4 hrs). Inappropriate discontinuation of IV insulin (44 vs. 8%, p=0.004), recurrent DKA (28 vs. 4%, p=0.05), and rebound hyperglycemic episodes (2.6± 3 vs. 1.1±1.7, p=0.045) occurred more frequently in the pre-PP group. No differences were observed for hypoglycemia, DKA complications, or hospital length of stay. We conclude that a DKA-PP that guides insulin infusion following acute DKA management and transition from IV to SC insulin therapy is effective at reducing frequency of recurrent DKA and rebound hyperglycemia without increasing frequency of hypoglycemia or complications.

1201-P

WITHDRAWN

1202-P

Vildagliptin, but Not Glibenclamide, Increases Circulating Endothelial Progenitor Cell Number: A 12-Month, Randomized, Controlled Trial in Patients with Type 2 Diabetes

ALESSANDRA DEI CAS, VALENTINA SPIGONI, RAFFAELLA ALDIGERI, MONIA CITO, ELISABETTA MARCHESI, MICHELA MARINA, ELEONORA DERLINDATI, IVANA ZAVARONI, RICCARDO C. BONADONNA, *Parma, Italy*

Fewer circulating endothelial progenitor cells (EPC) are a biomarker and, perhaps a mediator, of vascular damage, also in diabetes mellitus (DM). In short-term studies, uncontrolled for concomitant changes in glucose levels, DPP-4 inhibitors improved EPC bioavailability; however, the impact of long-term DPP-4-based therapies and the role, if any, played by glucose control are still unknown.

We conducted a randomized (2:1), open-label clinical trial to compare the effects of vildagliptin (V) (100 mg/day) vs. glibenclamide (G) (2.5 mg bid to a maximal dose of 5 mg bid) on circulating EPC following 4 and 12 months of treatment in 64 patients with type 2 DM (67% males), age 62±9 yrs (mean±SD), HbA1c 7.79±0.06%, disease duration 6.9±0.6 yrs and BMI 27.0±0.6 Kg/m^2 in Metformin failure (HbA1c≥7%). At baseline, after 4 and 12 months of intervention the main clinical/biohumoral parameters, concomitant therapies, EPC number (n°cells CD34$^+$/CD133$^+$/KDR$^+$ per 10^6 cytometric events) and plasma hsPCR, SDF-1α, IL-6 and BNP were assessed.

Baseline characteristics were comparable in the two groups (V n=40;G n=24). V and G similarly improved glucose control ($\Delta_{12\text{-}0}$ HbA1c%:-0.81±0.54 (V) vs. -0.79±0.78 (G);p=0.92). V significantly increased EPC number at 12 months (vs. baseline) compared to G ($\Delta_{12\text{-}0}$ EPC number: +17.6±1.0% (V) vs. -3.0±1.1% (G); p<0.05). BNP, IL-6 and hsPCR plasma levels were stable throughout the study in both groups. At 12 months, V significantly reduced SDF-1α plasma levels compared to G ($\Delta_{12\text{-}0}$ SDF-1α: -25.7±5.2% (V) vs. +6.7±7.9% (G); p<0.001).

Thus, vildagliptin exerts a beneficial long-term effect on EPC levels, at glycemic equipoise, with a putative positive effect on vascular integrity. The V-induced reduction in plasma SDF-1α levels may not reflect bone marrow microenvironment and might be desirable in light of the emerging role of circulating SDF-1α as an independent cardiovascular risk biomarker. (NCT01822548).

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1203-P

Renal Outcomes Associated with Alogliptin vs. Placebo in Patients with Type 2 Diabetes Mellitus and Recent Acute Coronary Syndrome: Results from the EXAMINE Trial

MUTHIAH VADUGANATHAN, WILLIAM B. WHITE, DAVID M. CHARYTAN, CRAIG WILSON, STUART KUPFER, LANYU LEI, YUYIN LIU, FAIEZ ZANNAD, CHRISTOPHER P. CANNON, GEORGE L. BAKRIS, *Boston, MA, Farmington, CT, Deerfield, IL, Nancy, France, Chicago, IL*

Background: Patients with type 2 diabetes mellitus (T2DM) are at higher risk of developing chronic kidney disease (CKD) and progressing to dialysis vs. nondiabetic patients. We evaluated the effects of the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin on CKD progression in the EXAMINE trial.

Methods: CKD endpoints, including creatinine doubling and dialysis initiation, were assessed in patients with T2DM and recent acute coronary syndrome (within 15-90d) randomized to alogliptin (n=2701) or placebo (n=2679). Those receiving dialysis within 14 days were excluded.

Results: Median follow-up was 18mo. Baseline characteristics were balanced in both groups (age 61 years; 68% male; 71% with eGFR ≥60 mL/min/1.73m^2). Compared with placebo, alogliptin did not significantly affect rates of CKD progression, albuminuria change, or dialysis initiation. In follow-up, changes in renal laboratory parameters on alogliptin were comparable to that of placebo (Table).

Conclusions: In EXAMINE, the DPP-4-inhibitor, alogliptin, when added to standard of care, was comparable to placebo on CKD progression. Longer-term renal evaluation of DPP-4 inhibitors is required. (NCT00968708).

Table. Renal Clinical Endpoints in Alogliptin and Placebo Groups in the EXAMINE Trial.

Adverse Events	Alogliptin N = 2701	Placebo N = 2679	P-value
Composite Renal Adverse Events	609 (22.5)	585 (21.8)	0.531
CKD progression	62 (2.3)	69 (2.6)	0.505
Albuminuria (>300 mg/day)	30 (1.1)	39 (1.5)	0.261
Microalbuminuria (30-300 mg/day)	32 (1.2)	21 (0.8)	0.137
Acute renal failure	43 (1.6)	38 (1.4)	0.601
Composite Renal Serious Adverse Events	97 (3.6)	88 (3.3)	0.537
Acute renal failure	43 (1.6)	36 (1.3)	0.449
Initiation of Dialysis	24 (0.9)	22 (0.8)	0.789
Abnormal Renal Function in Follow-up			
SCr increase ≥2x from baseline	18 (0.7)	17 (0.6)	0.888
SCr >2.0 mg/dL	96 (3.6)	96 (3.7)	0.945
eGFR decrease >25% from baseline[b]	209 (7.9)	201 (7.7)	0.759
eGFR decrease >50% from baseline[b]	24 (0.9)	24 (0.9)	0.973

Abbreviations: eGFR = estimated glomerular filtration rate; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SCr = serum creatinine

[a] Patients with at least one post-discharge renal laboratory parameter available for analysis
[b] eGFR calculated based on the Modification of Diet in Renal Disease formula

Supported By: Takeda Development Center Americas, Inc.

1204-P

Combined Administration of a Long-Acting Glucagon-like Peptide-1 (GLP-1) Receptor Agonist with FXR Agonist Obeticholic Acid (OCA) Exerts Benefits on Aspects of Nonalcoholic Steatohepatitis (NASH) in Mice

HANI JOUIHAN, SARAH WILL, SILVIA GUIONAUD, PETER RAVN, JAMES L. TREVASKIS, *Gaithersburg, MD, Cambridge, United Kingdom*

NASH, a rapidly growing epidemic, is associated with the presence of diabetes and obesity. Currently there are no approved therapies for NASH, however OCA and GLP-1 receptor agonists are leading candidates. Here we explored the effects of a long-acting GLP-1 receptor agonist, IP118, alone or in combination with OCA in an obese mouse model of NASH. Lep^{ob}/Lep^{ob} mice were fed a diet high in trans-fat (40%), fructose (22%) and cholesterol (2%), or control low-fat diet for 8 weeks, and then randomized to the following treatment groups: vehicle, IP118, OCA (0.05% in NASH diet, ~30 mg/kg/d) or IP118 + OCA for 4 weeks. Mice on test diet for 12 weeks exhibited hallmark features of NASH (enhanced steatosis, fibrosis, and elevated ALT). Treatment with OCA did not alter body weight, whereas IP118 induced 4.3% weight loss, and the addition of OCA did not further enhance weight loss (3.5%). Administration of OCA reduced liver weight and liver lipid (both by 17%) but did not change plasma ALT levels. In contrast, IP118 reduced liver weight (26%), liver lipid (15%) and ALT (29%) while combination therapy modestly enhanced these effects by further reducing liver weight (35%), liver lipid (22%) and ALT (39%). Histopathologically, IP118 and IP118 + OCA reduced steatosis and tended to reduce inflammation. Fibrosis was increased by NASH diet, and not altered by IP118 or OCA alone. Combination IP118 + OCA group exhibited less fibrosis and was not different from Lep^{ob}/Lep^{ob} mice on control diet. Hepatic gene profiling showed that IP118 and IP118 + OCA, but not OCA alone, increased expression of genes controlling mitochondrial function and oxidative capacity (Mfn1, Tfam, Sirt1, Cpt1a). Together, these data suggest a complementary effect of GLP-1 receptor agonism plus OCA treatment on attenuating hepatosteatosis and fibrosis at least partly via enhanced mitochondrial function.

1205-P

The Antisteatotic Effect of Metformin Involves Enhanced Leptin Sensitivity via Increased Hepatic Expression of Leptin Receptors

LIXIA GAN, *Chongqing, China*

In addition to the ascertained efficacy as antidiabetic drug, Metformin is increasingly being used as weight-loss agent in obesity, and as insulin sensitizer in nonalcoholic fatty liver disease (NAFLD). However, the mechanisms underlying these effects are still incompletely understood. Emerging evidence suggest Metformin as leptin sensitizer to mediate the weight-loss effect in the brain. In this study, we investigated effects of Metformin on peripheral expression of leptin receptors in liver and kidney in mice. C57BL/6 mice were fed with chow or high-fat diet (HFD) for 5 months. Afterwards, mice were treated with Metformin (50mg/kg or 200mg/kg) for 15 days. Metabolic parameters and hepatic gene expression were analyzed at the end of the treatment. We also tested the effects of Metformin on plasma sOB-R levels in newly diagnosed T2DM patients and mice, and assess its effect on hepatosteatosis. Results showed that Metformin up-regulates the expression of leptin receptors (OB-Ra, -Rb, -Rc, and -Rd) in liver but not

For author disclosure information, see page A696.

in kidney. The stimulation effect is dose-dependent in both chow and HFD mice. Upregulation of OB-Rb, long signaling isoform, nevertheless, needs higher dose of Metformin. This effect was paralleled by increased soluble leptin receptor (sOBR) levels and decreased hepatic triglyceride content and lipogenic gene expression, including sterol regulatory element binding protein 1c (SREBP-1c), fatty acid synthase (FAS) and HMG-CoA reductase. Taken together, these data identify hepatic leptin receptor as target gene being up-regulated by Metformin which may enhance leptin sensitivity in liver to alleviate steatosis. Thus, these results may provide novel rationale in future clinical studies of Metformin on leptin-resistance associated disorders.

Supported By: National Natural Science Foundation of China (81270482)

1206-P

Dopamine Agonist Therapy Reduces Elevated Heart Rate and Dysglycemia in Type 2 Diabetes Subjects

BINDU CHAMARTHI, AARON I. VINIK, MICHAEL EZROKHI, ANTHONY H. CINCOTTA, *Boston, MA, Norfolk, VA, Tiverton, RI*

Elevated sympathetic tone contributes to both cardiovascular disease (CVD) and dysglycemia via pleiotropic mechanisms including increasing resting heart rate (RHR) and insulin resistance. Several studies have reported a strong association between elevated RHR and CVD risk, particularly at RHR ≥70 beats per minute (BPM). Bromocriptine-QR (BQR) is a sympatholytic dopamine D2 agonist, insulin sensitizer approved for the treatment of type 2 diabetes (T2D) observed to reduce CVD. We investigated the effect of BQR on RHR and the relationship of this effect with its glycemic control effect in T2D subjects from the Cycloset Safety Trial with baseline HbA1c ≥7.5% on 1-2 oral hypoglycemic agents with no concomitant diabetes or blood pressure (BP) medication change at 24 weeks. RHR was obtained from an ECG. Multivariate regression and categorical analyses with cutoffs at baseline RHR (bRHR) < or ≥ 70 BPM were conducted. Among subjects with bRHR ≥ 70 (N=61 BQR, 30 placebo (P); 2:1 randomization), multivariate regression revealed that bRHR is a significant positive predictor of BQR (but not P) induced RHR reduction (β = -0.30, P=0.02). BQR reduced RHR by 5.5 BPM vs. P in subjects with bRHR ≥70 (mean RHR change: -4 BPM BQR, 1.5 BPM P; p=0.003) and by 9 BPM in subjects with bRHR ≥80 (N=32; mean RHR change: -7 BPM BQR, 2 BPM P; p=0.004) without change in BP. With bRHR < 70 (N=92) there was no significant within or between group change in RHR. Analysis of HbA1c reduction as a function of bRHR demonstrated HbA1c reductions with BQR vs. P as follows: < 70 BPM: - 0.62 (P=0.009); ≥ 70 BPM: -0.71 (P=0.007), ≥ 80 BPM: -1.13 (P=0.01). Furthermore, in subjects with bRHR ≥70, multivariate regression analyses demonstrated that the magnitude of RHR reduction is an independent predictor of the magnitude of HbA1c reduction with BQR but not P therapy (β = 0.47, P=0.001). These findings support a sympatholytic mechanism for 1.) BQR induced reduction of both RHR and HbA1c in subjects with elevated RHR and 2.) BQR's demonstrated impact to lower CVD events.

1207-P

Effects of Acute and 12-Week Incretin-based Therapy on Renal Uric Acid Clearance in Type 2 Diabetes

MARCEL H. MUSKIET, LENNART TONNEIJCK, MARK M. SMITS, MARK H. KRAMER, MICHAELA DIAMANT, JAAP A. JOLES, DANIËL H. VAN RAALTE, *Amsterdam, Netherlands, Utrecht, Netherlands*

Increased serum uric acid (SUA) is associated with gout, kidney stones and renal and cardiovascular disease in type 2 diabetes (T2D). Incretin-based therapies, i.e., GLP-1 receptor agonists (RA) and DPP-4 inhibitors, exhibit pleiotropic effects including natriuresis and alkalization of urine. Whereas linagliptin in T2D patients and native GLP-1 in diabetic rats reduce SUA, the effects of GLP-1RA on SUA and the role of renal UA clearance is unknown. Fifty-seven T2D patients (age 63±7 years, BMI 31.8±4.1 kg/m^2, eGFR 95±20 mL/min/1.73m^2, SUA 335±70 µmol/L) were randomized to acute exenatide or placebo infusion. Then, patients were randomized to 12-week treatment with liraglutide, sitagliptin or matching placebos. We determined SUA, absolute and fractional (inulin-corrected) excretion of UA and sodium, urinary pH, blood and urinary glucose, insulin and mean arterial pressure (MAP). Baseline absolute and fractional UA excretions were 2226±96 nmol/min/1.73m^2 and 8.8±0.3%, respectively. Exenatide infusion did not affect SUA compared to placebo, however it increased absolute UA excretion by 564±175 nmol/min/1.73m^2 (P=0.003) and fractional UA excretion by 1.0±0.4% (P=0.011). Also, exenatide increased sodium excretion, urinary pH, insulin and MAP, and reduced blood glucose (P<0.05). No patient showed glycosuria. In multivariable regression, exenatide-induced UA excretion was largely explained by changes in urinary pH and, in part, by sodium excretion. Plasma glucose, insulin and MAP did not influence the effect of exenatide on UA excretion. Neither 12-week liraglutide nor sitagliptin treatment affected SUA, UA excretion, sodium excretion or urinary pH. Although acute exenatide infusion does not affect SUA in T2D with normal baseline UA levels, it stimulates UA excretion, likely by increasing urinary pH which reduces tubular UA reabsorption, although UA formation was not assessed. Twelve-week liraglutide or sitagliptin treatment does not affect SUA or renal UA clearance in T2D.

Supported By: European Community's Seventh Framework Programme (FP7/2007-2013)

1208-P

RVX-208 Affects Epigenetics to Lower Major Adverse Cardiovascular Events (MACE) in Atherosclerotic Patients and Especially in Ones with Diabetes Mellitus

EWELINA KULIKOWSKI, SYLWIA WASIAK, DEAN GILHAM, CYRUS CALOSING, LAURA TSUJIKAWA, CHRISTOPHER HALLIDAY, JAN JOHANSSON, MIKE SWEENEY, NORMAN C. WONG, *Calgary, AB, Canada, San Francisco, CA*

Apabetalone (RVX-208) inhibits Bromodomain and Extra-Terminal (BET) proteins by displacing their natural ligand, acetylated lysine that populate histone tails. Ligand bound BET proteins recruit transcriptional machinery to DNA and thereby modify gene activity. Patients with cardiovascular disease (CVD, n=499), in phase IIb trials SUSTAIN and ASSURE, given RVX-208 had a 55% relative risk reduction (RRR) in MACE vs. placebo. In diabetes mellitus (DM) patients, RVX-208 lead to a 77% RRR in MACE. RVX-208 raises ApoA-I and high density lipoprotein (HDL) by 7.5 and 3 mg/dL (p<0.05), respectively, but these modest changes do not explain the marked MACE reduction thus leading us to study RVX-208 effects beyond lipids. Plasma glucose in DM patients (n=192) was unchanged given RVX-208 or placebo, except in those (n=119) with low HDL <40 mg/dL, RVX-208 lowered glucose by -0.3 vs. +0.9 mmol/L in placebo. Microarray surveys of primary human hepatocytes (PHH) exposed to RVX-208 had decreased gene expression in several pathways linked to CVD risk with marked downregulation in 19/26 complement and 20/33 coagulation genes. These microarray data were confirmed in hepatocytes by measuring mRNA levels and secreted protein. Next, selected key proteins in affected pathways were assayed in plasma of trial patients and noted to be reduced 4-14% by RVX-208 vs. baseline. Additionally, in PHH RVX-208 suppressed by 25% the mRNA encoding flavin monooxygenase-3 (FMO3), a key hepatic enzyme in the pathogenesis of DM and CVD. Human whole blood (WB) exposed ex-vivo to RVX-208 affected many genes with defined roles in atherogenesis, i.e., suppression of 37/46 pro-atherogenic but induction of 8/18 anti-atherogenic genes. Additionally, RVX-208 suppressed expression of 30 cytokines in WB. In summary, RVX-208 reduces MACE in CVD patients and especially in those with DM. RVX-208 acts by modulating cellular epigenetics which in turn affect multiple biological processes that underlie CVD and DM.

1209-P

Gastric Electrical Stimulation and Pyloroplasty as the Optimal Therapeutic Strategy for Diabetic Gastroparesis

IRENE SAROSIEK, BRIAN DAVIS, YVETTE GOMEZ, TAMIS BRIGHT, RICHARD W. MCCALLUM, *El Paso, TX*

Background: Gastroparesis (GP) symptoms can be reduced by 60% in diabetic (DM) patients treated with gastric electrical stimulation (GES), without acceleration of gastric emptying (GE). This therapeutic deficiency was addressed by adding pyloroplasty (PP) as a supplementary surgery in DMGP patients receiving GES. Our aim was to assess the long term efficacy and safety of combining surgical PP with GES, and to investigate GE changes in DM patients.

Methods: Combining GES and PP surgery was performed with use of a robotic system in 28 patients, and (64%) were DM. Total GP symptoms scores (TSS) assessing severity of nausea, early satiety, bloating, vomiting, postprandial fullness, epigastric pain, were obtained by using a 5-point Likert scale at baseline and at last F/U visit. The 4-hrs scintigraphy GE test was conducted before surgery and at F/U visits where GP was defined as > 60% retention of isotope at 2 hrs and >10% at 4 hrs.

Results: Post-op data from 13 DM GP patients were available. GES plus PP improved TSS by 76% [(mean 3.3 vs. 0.94 points P<0.0001). After surgery, the mean retention GE was decreased by 54% at 2 h (77% vs. 36%) and 58% at 4h (54% vs. 23%), while 62% of DMGP actually normalized their GE. There was significant reduction in days of hospitalization from 78 (0-240) to 10 days/patient (0-30). There were not post-surgical complications or technical problems related to GES system observed during the long term follow up.

Conclusions: 1.) Diabetic GP drug-refractory patients receiving both GES and PP improved their symptoms by 76%, more than achievable by GES alone, while significantly accelerating rate of gastric emptying. 2.) The combination of two surgical approaches: GES and PP, addresses both the subjective and objective goals in treating diabetic gastroparesis.

HEALTH CARE DELIVERY—ECONOMICS

Moderated Poster Discussion: Diabetes Care in 2016—Evaluations of Barriers and Facilitators of Novel Care Delivery *(Posters: 1210-P to 1217-P), see page 14.*

1210-P

Barriers to Effective Primary Care among Patients with Poorly Controlled Type 2 Diabetes

CINDY D. ZAMUDIO, MICHELLE VO, CONNIE S. URATSU, ANDREA ALTSCHULER, MICHELE HEISLER, RICHARD W. GRANT, *Oakland, CA, Ann Arbor, MI*

Effective management of type 2 diabetes can be a challenge in primary care practice due to time constraints and competing demands. We are conducting an NIH-funded trial for patients with poorly controlled diabetes. Intervention patients are provided the opportunity to prepare for upcoming primary care visits by choosing their 1 or 2 highest-priority concerns for that visit. Intervention patients can choose priorities from the following 5 categories: diabetes-related, new/important health issues, nondiabetes medications, important life changes, and mood/motivation issues. Here we present baseline primary care provider (PCP) survey results and initial findings regarding patient pre-visit priorities among intervention arm patients. In the baseline PCP survey (97% response rate, 141 of 146 PCPs), the majority of PCPs (84%) reported insufficient time during visits and 41% reported that they were often unable to address all their visit agenda items in a single visit. Common PCP-perceived barriers included patients not being prepared to discuss their top 1 or 2 concerns (43%) or raising concerns at the end of the visit (39%). Intervention patients (n = 116, age 61 ± 10 years, 52% women, 29% non-white, mean % A1c 9.1 ± 1) have submitted 183 specific pre-visit concerns for 116 visits to date as part of the clinical trial. Less than half of visits (55/116, 47%) included diabetes as a top concern. Among visits with nondiabetes related concerns, 19% (34/116) prioritized important life changes and/or mood/motivation issues. These results underscore the challenges to primary care of diabetes, including difficulty coordinating patient-provider visit agendas and prevalence of nondiabetes related concerns. Improving glycemic control in primary care may require that patients' nondiabetes related priorities are identified and addressed before diabetes management changes can be successfully implemented. (NCT02375932).

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1211-P

The Impact of Electronic Consultation (EC) on Glycemic Control in Type 2 Diabetes (T2D)

ELENA M. MORARIU, ARCHANA BANDI, FREDERICK DERUBERTIS, R. HARSHA RAO, *Pittsburgh, PA*

EC is used to enhance access to specialty care at the VA Pittsburgh Healthcare System for T2D patients at Community Based Outpatient Clinics and spoke facilities. However, the impact of EC on clinical outcomes in T2D is unknown. We define EC as asynchronous specialist-provider and specialist-patient communication without face-to-face contact. The EC process involves chart review and patient interview by phone to formulate recommendations with patient input (engagement), and convey them to the PCP electronically. Subsequent follow-up for a period of ~3mo depends on patient willingness to participate and complete the EC process (*completion*). We used retrospective chart review to assess the impact of EC on HbA1c at ~3mo after initial EC contact, and sustainability ~1 yr after last EC contact in 201 patients, based on Full Engagement to Completion (FE+C, n 79), Partial Engagement without Completion (PE-C, n 76), or Initial Engagement Only (IEO, n 43) who received one time recommendations only. We also estimated other benefits of EC, using travel distance, time, and cost saved. The impact of EC on HbA1c was both immediate (Mean±SE: Before EC 9.2±0.1; At 3mo 8.4±0.1; Difference [ ] 0.9±0.1, p<0.0001) and sustained at 1 yr (8.4±0.1, 0.9±0.1, p<0.0001). The greatest improvement was seen in FE+C patient at both 3mo (HbA1c change FE+C 1.2±0.2, p<0.0001), compared to both PE-C (0.5±0.2, p<0.005) and IEO (0.8±0.3, p= 0.005), and at 1 yr (HbA1c change FE+C 1.3±0.2, p<0.0001; PE-C 0.6±0.2, p<0.005; and 0.5±0.3, p =0.07). Mean savings/EC "visit" were 124.5±68.1 mi of travel, 2.8h±1.4h of time, and $67.2±36.8 in travel costs. Glycemic benefits from EC are greatest and most sustained with full patient engagement to completion. The benefit with partial engagement is modest but sustained, but that with one-time recommendations is short-lived and dissipates over time, suggesting that full engagement by the patient is required for sustained benefit. EC is an effective option in T2D for expanding access to specialty care.

1212-P

Effect of Smartphone-based Glucose Monitoring and Feedback System on Diabetes Management in Multiple Private Clinics Setting

YEOREE YANG, JOONYUB LEE, BORAMI KANG, HAE KYUNG YANG, EUN YOUNG LEE, SEUNG-HWAN LEE, KUN-HO YOON, BONG-YUN CHA, JAE-HYOUNG CHO, *Seoul, Republic of Korea*

Recent studies have reported the effectiveness of internet based diabetes management, and now the area is expanded to the smartphone based system. However almost research was based on tertiary hospital or professional diabetes clinics. This research is purposed to validate the utility of smartphone based glucose monitoring system in the private clinic setting. In this multicenter, cluster-randomized and prospective study, we enrolled the 13 private clinics in Seoul and other local large cities in Korea. 150 subjects from 9 institutions and 97 subjects from 4 institutions were assigned to intervention and control group, respectively. The intervention group was monitored by smartphone. When patient checked the glucose level and inputted the results into the smartphone, and then the smartphone transmitted the data to the main server. Every week, the doctor checked the patient's glucose results and sent the feed-back massage. The control group received the general lifestyle modification education and out-patient clinic consultation every month. Both group received the blood test at baseline and 3-month follow-up. At 3-month, greater reduction in mean HbA1c level was observed in the intervention group (-0.63 ± 0.82%, p<0.0001) compared with control group (-0.27 ± 0.71%, p= 0.0006). And this was greater in patient with higher baseline HbA1c level (≥ 8.0%, intervention group; -1.06 ± 0.82%, p<0.001 vs. control group; -0.25 ± 0.82%, p=0.1692). FPG was also significantly reduced in the intervention group (-18.86 ± 63.35 mg/dL, p <0.0001) compared with control group (-2.33 ± 53.67 mg/dL, p =0.8227). In addition, significant reduction was also observed in diastolic BP, body weight and body mass index. In conclusion, smartphone based glucose monitoring and feed-back system was effective when applied to the private clinic setting. Even the general doctor could effectively utilize this system, it could be applied to the diverse institutions and patients.

1213-P

Cost-Effectiveness of Alternative GDM Screening Protocols Including Maternal Follow-up to Prevent T2D

SIMON J. NEUWAHL, ANDREA J. SHARMA, HENRY S. KAHN, SUZANNE M. GILBOA, JENNIFER L. WILLIAMS, THOMAS J. HOERGER, MEDA E. PAVKOV, PING ZHANG, *Research Triangle Park, NC, Atlanta, GA*

Women diagnosed with gestational diabetes (GDM) and their infants are at substantially higher risk of perinatal complications. Women with GDM are also at high risk for developing T2D postpartum and could benefit from an intensive lifestyle intervention as demonstrated by the Diabetes Prevention Program (DPP). Two protocols for GDM screening and diagnosis have been widely recommended. Carpenter and Coustan (C&C) uses a two-step screening strategy with a preliminary glucose challenge test for all women and a follow-up glucose tolerance test for those deemed at risk, whereas the International Association of Diabetes and Pregnancy Study Groups (IADPSG) uses a one-step strategy which requires a glucose tolerance test for all women and identifies up to 4 times as many women. We constructed a probabilistic simulation model to examine the cost-effectiveness of screening for and treating GDM at 24-28 weeks of gestation followed by the referral of mothers with GDM to a postpartum lifestyle intervention. We compared the C&C and IADPSG screenings to a no-screening scenario and to each other. The T2D risk reduction associated with the DPP-like intervention was adjusted to represent real-world effectiveness, not clinical trial efficacy. We assumed participation among postpartum women was low given the competing demands of new motherhood. Compared to the no-screening scenario, both GDM screening strategies were cost-saving. Compared to the two-step C&C approach, the one-step IADPSG approach might be considered cost-effective (incremental cost-effectiveness ratio of $19,000/QALY). Results were particularly sensitive to assumed reductions in high-cost perinatal outcomes such as neonatal intensive-care unit admissions as well as assumptions about the effectiveness and uptake of a postpartum intensive lifestyle program. The cost-effectiveness of the GDM screening strategies improves substantially with more effective lifestyle programs and greater program uptake following birth.

Supported By: Centers for Disease Control and Prevention

1214-P

Diabetes Prevention among Women of Reproductive Age: A Missed Opportunity?

CASSONDRA MARSHALL, SARA R. ADAMS, JULIE A. SCHMITTDIEL, *Oakland, CA*

For women of reproductive age, the preconception period is a crucial time to focus on chronic disease prevention, and to improve the outcomes of future

For author disclosure information, see page A696.

pregnancies. However, little is known about diabetes prevention clinical practice for this group. Using electronic health record (EHR) data from patients at Kaiser Permanente Northern California, we identified 272,204 adults with incident prediabetes (PDM) (FPG=100-125 or A1c=5.7-6.4) between 2007-2010, including 22,013 women of reproductive age (18-44). We looked for evidence of "clinical recognition" of PDM in the EHR in the 6 months post-lab, defined as one or more of the following: re-testing of blood glucose levels, referral or attendance to health education/nutrition services, diagnosis of PDM, Metformin initiation, or a clinical note of discussion of PDM. We used multivariate logistic regression to examine the relationship between clinical recognition and patient gender and age, including a variable for women 18-44. Models were adjusted for race/ethnicity, BMI, index FPG/A1c value, and geocoded census block measures of poverty and educational attainment. Pregnant women were excluded from the analysis. In the 6 months following PDM incidence, 13.7% of women 18-44 had their blood glucose retested, 12.9% received a PDM diagnosis, <1% initiated Metformin, 6.8% were referred to or attended health education, and 31.1% had PDM documented in notes. Compared to women 45 and older, women of reproductive age had lower odds of having any clinical recognition (AOR: 0.9; 95% CI: 0.9-0.9), but a higher odds of referral to health education (AOR: 1.3; 95% CI: 1.2-1.3). Women 18-44 were less likely than men 18-44 to have PDM in notes (AOR: 0.9; 95% CI: 0.8-0.9). Low clinical recognition of PDM for women of reproductive age compared to men of the same age and older women suggests there are missed opportunities for diabetes prevention among this vulnerable population. Future research should focus on improving awareness of diabetes risk among young women and their clinicians.

Supported By: Agency for Healthcare Research and Quality

1215-P

Risk Factors Associated with 30-Day Readmission and Length of Stay in Patients with Type 2 Diabetes

CHRISTOPHER S. HOLLENBEAK, LAURA ENOMOTO, MEREDITH B. ROSENTHAL, DEEPIKA SHRESTHA, ROBERT A. GABBAY, *Hershey, PA, Cambridge, MA, Lancaster, PA, Boston, MA*

Patients with type 2 diabetes (T2DM) are at greater risk of 30-day readmission. The purpose of this study was to determine factors associated with 30-day hospital readmission and length of stay (LOS) for patients with and without T2DM. We studied all inpatient admissions in Pennsylvania during 2011 using data from the Pennsylvania Health Care Cost Containment Council. T2DM was identified using primary and secondary ICD-9 diagnosis codes. Primary outcomes were readmission within 30 days of discharge and inpatient LOS. Logistic and generalized linear regression models were fit to readmission and LOS, respectively, to study the effect of T2DM, controlling for relevant covariates. Propensity score matching was used to deal with covariate imbalance. Determinants of 30-day readmission and LOS among patients with diabetes were also studied. Among inpatient admissions, patients with diabetes were more likely to be readmitted (AOR=1.17, p<0.001) and have longer LOS (0.19 days, p<0.001) compared to patients without diabetes. Among patients with diabetes, several factors were associated with readmission, including demographics, source of admission, and comorbidities. Patients with diabetes were more likely to be readmitted for infectious complications (9.4% vs. 7.7%), heart failure (6.0% vs. 3.1%), and chest pain/MI (5.5% vs. 3.3%) than patients without diabetes. Comorbidities were the most important determinants of LOS among patients with diabetes, particularly dementia (1.43 days, p<0.001) and hemi/paraplegia (2.26 days, p<0.001). Diabetes is associated with both risk of 30-day readmission and LOS, and several patient specific factors are associated with outcomes for patients with diabetes. Future studies should develop strategies to reduce unnecessary readmissions and decrease LOS.

1216-P

Effect of Medication Reconciliation on Emergency Department Visits and Hospitalizations in Patients with Diabetes

ALEXANDER TURCHIN, OLUKAYODE SOSINA, HUABING ZHANG, MARIA SHUBINA, SONALI P. DESAI, DONALD C. SIMONSON, MARCIA A. TESTA, *Boston, MA, Baltimore, MD, Beijing, China*

Medication reconciliation is one of The Joint Commission's National Patient Safety Goals. However, patient outcomes after medication reconciliation remain uncertain. Patients with diabetes (DM) are at high risk from medication errors as adverse drug events stemming from use of DM medications commonly lead to ED visits and hospitalizations.

We retrospectively studied adults with DM treated in primary care clinics affiliated with two academic medical centers between 2000 and 2014. We analyzed the relationship between ambulatory reconciliation of DM medications (individual medication review by a clinician) over a 6-month treatment assessment period and frequency of ED visits and hospitalizations over the subsequent 6-month outcome assessment period (a single patient could contribute multiple assessment periods).

Among 261,765 study periods representing 31,689 patients, 176,274 (67.3%) had all, 27,775 (10.6%) had some and 57,716 (22.1%) had no DM medications reconciled. Over the subsequent 6-month outcome assessment period patients with all, some or no DM medications reconciled had 0.223, 0.232 and 0.230 ED visits, respectively (p = 0.0296). Over the same period of time, patients with all, some or no DM medications reconciled had 0.132, 0.145 and 0.154 hospitalizations, respectively (p < 0.0001). In multivariable analysis adjusted for clustering within patients, comparing to patients with no DM medications reconciled, patients with some medications reconciled had fewer ED visits (-0.056 visits/6 months; p = 0.037) and hospitalizations (-0.076; p = 0.026). Patients with all DM medications reconciled had fewer ED visits (-0.041; p = 0.018); the effect on hospitalizations did not reach significance (-0.027; p = 0.22).

Patients who had at least some of their DM medications reconciled had lower healthcare utilization. Medication reconciliation could therefore contribute not only to improving patient safety but also to lowering costs of care.

Supported By: Patient-Centered Outcomes Research Institute

1217-P

Sweet Transitions: Coordinating Diabetes Care between Hospital and Primary Care Settings

GEORGINA G. POLANCO, ADELE E. CORBIN, ERIN M. SISSON, KATHI B. SMITH, SUSAN D. BRUMM, DAVID A. D'ALESSIO, MERCEDES FALCIGLIA, *Cincinnati, OH*

Hospitalized patients with diabetes frequently have poor coordination of care at the time of discharge. Specifically, important information about diabetes care during hospitalization is often not communicated to outpatient caregivers since diabetes is rarely the primary reason for admission. We conducted a pilot study of an intervention, Sweet Transitions (ST), to coordinate diabetes care between hospital and ambulatory settings. Patients with diabetes and poor control (A1c ≥ 9.0%) hospitalized at a 600-bed academic hospital (UCMC) and the affiliate VA were enrolled. The ST intervention consisted of education before discharge, phone follow-up 24-72h after discharge, and a subsequent visit with a nurse practitioner with expertise in diabetes care. During this transition period, patients received education and insulin or oral medication adjustment as often as needed by phone or in-person. Once a treatment plan was established, patient information and care was transferred to the clinician responsible for their diabetes management. Readmissions (30-day) for ST patients were compared to those of discharged patients with diabetes who did not receive the intervention, and A1c measurement was assessed before and after ST intervention. Ninety patients (50 UCMC, 40 VA, 75% male, mean age 58 years) were enrolled in the ST program for 42 ± 5 days. In 61 patients with repeat A1c measurement after 114 ± 6 days, values decreased significantly from 11.5 ± 0.2 to 9.1 ± 0.3% (p <0.001). A decrease in A1c of 3.8 ± 0.7% was observed in insulin naïve patients (p<0.001); findings were similar at both hospitals. The 30-day readmission rates were lower in the ST cohort (UCMC 6% vs. 18%, p=0.024; VA 10% vs.14%, NS). The ST intervention in hospitalized patients with poorly-controlled diabetes was associated with improved glycemic control and 30-day readmission rates after discharge. Interventions to ensure the sustainability of improved outcomes require further study at the primary care and community levels.

Moderated Poster Discussion: From Efficacy to Effectiveness—Evaluations of Real-World Prescribing Patterns in Adults with Diabetes
(Posters: 1218-P to 1225-P), see page 15.

1218-P

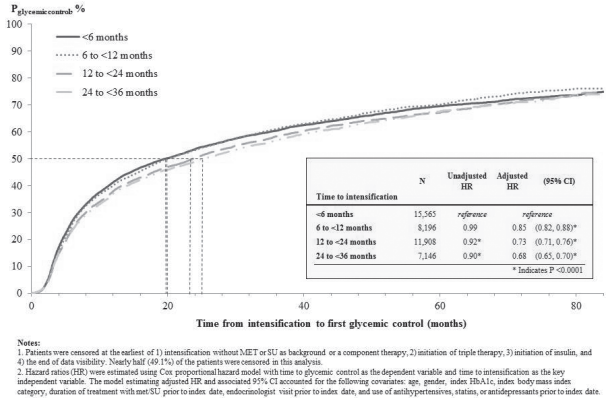
Time to Treatment Intensification and Its Association with Subsequent Glycemic Control among Patients with Type 2 Diabetes

URVI DESAI, NOAM Y. KIRSON, JENNIFER KIM, KAMLESH KHUNTI, SARAH B. KING, ERICH TRIESCHMAN, MICHAEL HELLSTERN, PHILLIP R. HUNT, JAYANTI MUKHERJEE, *Boston, MA, Gaithersburg, MD, Leicester, United Kingdom, Lexington, MA, Wallingford, CT*

This study assessed the association between timing of treatment intensification and subsequent glycemic control (first HbA1c <7% after intensification) among patients with type 2 diabetes using the UK Clinical Practice Research Datalink (1/2000 - 12/2014). The first record with HbA1c ≥7% after ≥3 months of Metformin (met) or sulfonylurea (SU) monotherapy was the index event. Intensification was defined as initiating ≥1 non-insulin antidiabetic medication in addition to met/SU after index. Of the 93,515 patients who met the study criteria (mean age: 60 years, ~59% male), 15,565 (17%) intensified <6 months after index, 8,196 (9%) after 6 to <12 months, 11,908 (13%) after 12 to <24

months and 7,146 (8%) after 24 to <36 months. Kaplan-Meier analysis found the median time to intensification to be 30.9 months. Earlier intensification was associated with shorter time to subsequent glycemic control: median time from intensification to control was 19.9, 20.4, 24.1 and 25.7 months respectively for patients intensifying <6, 6 to <12, 12 to <24 and 24 to <36 months after index. Using a Cox model to account for differences in baseline patient characteristics, the likelihood of attaining control further decreased as time to intensification increased (Figure 1). Additional research is needed to understand the long-term implications of delayed intensification.

Figure 1. Time to First Glycemic Control within Seven Years after Treatment Intensification Stratified by Time to Intensification.



Notes:
1. Patients were censored at the earliest of 1) intensification without MET or SU as background or a component therapy, 2) initiation of triple therapy, 3) initiation of insulin, and 4) the end of data visibility. Nearly half (49.1%) of the patients were censored in this analysis.
2. Hazard ratios (HR) were estimated using Cox proportional hazard model with time to glycemic control as the dependent variable and time to intensification as the key independent variable. The model estimating adjusted HR and associated 95% CI accounted for the following covariates: age, gender, index HbA1c, index body mass index category, duration of treatment with met/SU prior to index date, endocrinologist visit prior to index date, and use of antihypertensives, statins, or antidepressants prior to index date.

Supported By: Bristol-Myers Squibb; AstraZeneca

1219-P

Reduced Utilization of Health-Care Provider Resources with Automated Basal Insulin Titration in Patients with Type 2 Diabetes

JOCHEN SIEBER, HARPREET S. BAJAJ, KARRI VENN, RONNIE ARONSON, FRANK FLACKE, *Frankfurt, Germany, Brampton, ON, Canada, Toronto, ON, Canada*

Basal insulin titration in the real world is mostly guided by health care providers (HCP). Use of health information technology for insulin titration may offer similar glycemic effectiveness and lead to reduced utilization of HCP resources. LTHome (LTH) is a web tool that applies a rules engine-based algorithm for insulin titration. In a randomized trial, safety and efficacy of basal insulin glargine titration by LTH were compared to enhanced usual therapy (EUT [HCP-driven titration)] over a 3-month period with titration instructions provided throughout duration of the trial. Inclusion criteria were type 2 diabetes, age 18-75 years, computer literacy, and A1c >7.0%. 139 subjects with comparable baseline characteristics were randomized to LTH or EUT. At the end of trial period, A1c reduction (-1.0% and -1.1%; *P*=0.66) and hypoglycemia incidence were similar between groups. Significant difference in change of satisfaction scores favoring LTH was observed for Fear of Hypoglycemia Score (*P*=0.04) and Diabetes Distress Scale (*P*=0.04). Outside of scheduled study visits (4, 8, 12 weeks), significantly less patients required additional HCP visits in the LTH group compared to EUT (Table). In conclusion, automated basal insulin titration led to reduced HCP resource utilization and improved patient satisfaction, while obtaining similar glycemic safety and effectiveness. (NCT02540486).

Table.

No. of Patients	With Additional Visits	By Week 4	By Week 8	By Week 12
LTH (n=66)	None	61	60	60
	1	5	1	2
	> 1	0	0	0
EUT (n=65)	None	35	56	59
	1	13	5	5
	> 1	17	4	2
P for difference between groups		< 0.0001	0.0434	0.277

Supported By: Sanofi

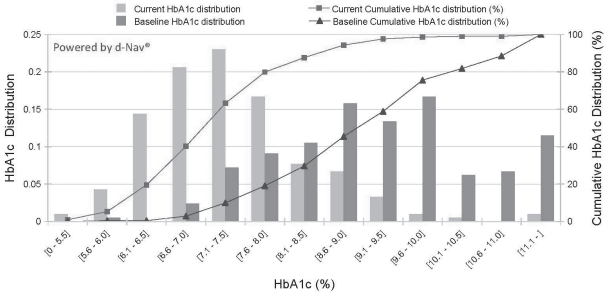
1220-P

Insulin Therapy Transformation in Northern Ireland

ROY HARPER, ROSEMARY DONNELLY, ISRAEL HODISH, *Belfast, United Kingdom, Ann Arbor, MI*

Managing population-based outcomes is a challenge for healthcare systems. In diabetes care there are several well-accepted measures including glycemic control, blood pressure and lipids. The South Eastern Health and Social Care Trust, Northern Ireland, provides care for ~2,500 patients with type 2 diabetes. While blood pressure and lipid profile goals have been achieved, A1c has been elevated, averaging 8.3% as of 2012. Since ~65% of our patients use insulin and average A1c in insulin users in the UK is high, we have implemented a collaborative effort to overcome the main barrier in insulin management, namely the need for frequent titration of dosage. Insulin users with inadequate A1c levels have been enrolled in the d-Nav® Insulin Guidance Service. d-Nav is a handheld device that analyzes stored glucose patterns and titrates insulin dosage weekly or more frequently as required, based on individual needs. The service includes nurse specialists who provide patients with ongoing support and clinical triage. From October 2012, >500 patients have been referred to the service (61 for >2 years). See Figure for reduction in A1c. The frequency of severe hypoglycemia was low at ~1.5 per 100 patient years with unsurpassed user satisfaction. Global implementation of such solutions has the potential to transform outcomes by optimizing long-term glycemic control, preventing morbidity and saving resources in the growing population who require lifelong insulin therapy.

Figure. Subscribers on d-Nav Service 9+ Month.



HbA1c Statistics

	Current	*Baseline*
#of patients	N=209	N=209
Average HbA1c (DCCT)	7.38%	9.36%
Standard deviation	1.05%	1.50%

1221-P

Association between Adherence to Glucose-Lowering Agents and Outcomes among Patients Age=65 with Type 2 Diabetes

KRISTINA S. BOYE, LUIS-EMILIO GARCIA-PEREZ, SARAH CURTIS, MAUREEN J. LAGE, *Indianapolis, IN, Delray Beach, FL*

Type 2 diabetes (T2D) is associated with high levels of morbidity and functional deterioration -especially among the elderly. Little data exists on this growing segment of the U.S. population and how this population segments' adherence to treatment may influence outcomes. This study examines the relationship between adherence to all glucose-lowering agents (GLA) and patient outcomes: costs, resource utilization, and complications. Data was provided by a large, Medicare supplemental (MarketScan) database from July 1, 2009 to June 30, 2014.

There were 123,235 T2D patients age ≥65 who received a GLA. Results (Table 1) illustrate that adherence, defined as proportion of days covered (PDC) ≥ 80%, was associated with significantly lower total all-cause medical costs, outpatient costs and acute care costs, compared to lower adherence thresholds (all p<0.001) over a 3 year period. Adherence was also associated with significantly lower probability of hospitalization or emergency room visit, shorter hospital length of stay and reduced odds of an acute complication (all p<0.001). Results suggest a total medical cost savings of $65,464 for every 1,000 patients who increased GLA adherence by simply 1%.

This study quantifies benefits to elderly patients in terms of decreased complications while healthcare payers realize lower costs as adherence to GLA improves.

Table 1. Association between Adherence and 3 Year Outcomes—Estimated Means from Multivariable Analyses*.

	Total Costs	Acute Care Costs	Outpatient Costs	Prescription Drug Costs	Probability of Hospitalization	Probability of ER Visit	Probability of Acute Complication
PDC >0% - <20%	$73,009*	$32,340*	$28,086*	$12,278*	56.22%*	72.09%*	24.11%*
PDC ≥20% - <40%	$57,887*	$24,507*	$22,625*	$10,666*	50.05%*	66.58%*	18.19%*
PDC ≥40% - <60%	$52,446*	$20,285*	$20,711*	$11,057*	45.45%*	62.40%*	16.26%*
PDC ≥60% - <80%	$48,284*	$16,664*	$19,265*	$11,911*	41.44%*	58.57%*	14.47%*
PDC ≥ 80%	$44,185	$13,373	$17,298	$13,381	37.43%	54.18%	13.02%

* - Comparisons between adherent (defined as PDC ≥ 80%) and non-adherence (PDC < 80%) all statistically significant. (P<0.001).

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1222-P

Validating Prescribing Choice in Older Patients with Type 2 Diabetes: An Economic Assessment of Patient Outcomes Using Routinely Collected Primary Care Data

JASON GORDON, PHIL MCEWAN, MARC EVANS, JORGE PUELLES, ALAN SINCLAIR, *Cardiff, United Kingdom, London, United Kingdom, Worcester, United Kingdom*

Prescribing for type 2 diabetes (T2D) should take into account estimates of economic value associated with alternative approaches to glycaemic control.

Using the CORE Diabetes Model, a cost-effectiveness analysis (UK perspective) evaluated intra-group changes in patient risk factor profiles associated with escalation to second-line treatment based on retrospective data from the UK Clinical Practice Research Datalink (CPRD) in patients with T2D ≥ 65 years. Lifetime costs and quality-adjusted life years (QALYs) were estimated for: Metformin (M) [control] and M + sulfonylurea (SU), dipeptidyl peptidase-4 inhibitor (DPP-4) or thiazolidinediones (TZD) [treatment arms]. Costs and utilities (discounted at 3.5% annually) were sourced from the literature.

At baseline, patients (n = 6,619) were approximately 72 years, with diabetes duration 6–7 years, weight of 86–90kg and HbA1c of 8%. At year 1, vs. baseline, weight increased with M+SU and M+TZD (0.60 and 1.28kg, respectively); weight decreased for M+DPP-4 (-1.21kg). M+SU, M+DPP-4 and M+TZD were associated with HbA1c changes of -1.02%, -0.76% and -0.57%, respectively. M+DPP-4 was associated with the largest QALY gain (control vs. treatment: 5.48 vs. 5.61; delta: 0.13) and a cost/QALY estimate of £21,318. M+SU was associated with a relatively small incremental cost (control vs. treatment: £19,228 vs. £19,507; delta: £279) and QALY gain (control vs. treatment: 5.34 vs. 5.36, delta: 0.02) and a cost/QALY of £17,640. M+TZD was cost-saving and associated with QALY gains, as small incremental treatment costs were offset by savings and benefits from complications avoided. The probability that M+DPP-4, M+SU and M+TZD following M was cost-effective, at a willingness to pay threshed of £30,000, was 61%, 54% and 74%, respectively.

Patients prescribed a DPP-4, SU or TZD following M were associated with health gains and economic analysis confirmed the cost-effectiveness of these prescribing decisions.

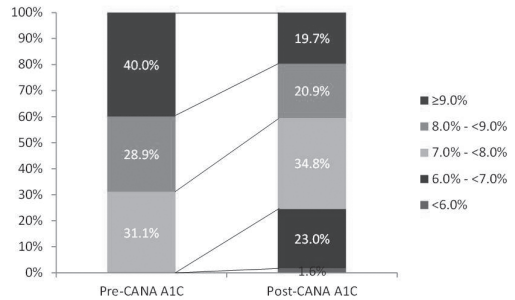
1223-P

Real-World 12-Month Outcomes of Patients with Type 2 Diabetes Mellitus (T2DM) Treated with Canagliflozin in a U.S. Managed Care Setting

WING CHOW, ERIN K. BUYSMAN, MARCIA F.T. RUPNOW, AMY J. ANDERSON, HENRY J. HENK, *Raritan, NJ, Eden Prairie, MN*

Canagliflozin (CANA), the first approved agent that inhibits sodium glucose co-transporter 2, improves glycemic control through an insulin-independent mechanism. This study evaluates glycemic control pre- and post-CANA over a 12 month period. This retrospective cohort study used data from a large U.S. health plan for adult commercial and Medicare Advantage enrollees with T2DM filling CANA between April 2013 - August 2014 who had A1c results pre and post the first observed CANA prescription and a pre-CANA A1c ≥7.0%. Of identified patients (n=2,269), 61% had CANA 100mg on the first observed fill, 41% were female, and mean age was 56 years. Pre-CANA mean A1c was 8.93% ±1.56%. Patients, on average, used 2.4 ±1.1 unique antihyperglycemic agents (AHAs) in the pre-CANA period, inclusive of injectables. Based on the last A1c result ≥30 days following the first observed CANA claim in the 12-month post-CANA period, patients had a mean reduction of 0.96% ±1.56%, with an average time to post-CANA A1c of 262 days. The proportion of patients achieving A1c <7.0% and <8.0% were approximately 25% and 59% post-CANA (Figure). CANA was prescribed to patients with T2DM who were often uncontrolled (mean pre-CANA A1c of 8.93%) despite prior treatment with multiple AHAs. Improvements in A1c consistent to those found in clinical trials were observed in the 12 months following the first CANA prescription.

Figure. Baseline and Follow-up A1c Values Pre- and Post-CANA in Patients with Pre-CANA A1c ≥7.0%.



1224-P

HbA1c Outcomes in Patients Treated with Canagliflozin vs. Sitagliptin in a U.S. Health Plan

SARAH W. THAYER, RICHARD AGUILAR, WING CHOW, *Eden Prairie, MN, Sisters, OR, Raritan, NJ*

A large proportion of persons with type 2 diabetes (T2DM) do not achieve adequate glycemic control and are at risk of developing chronic complications, despite the many treatment options available. Canagliflozin (CANA), a sodium glucose co-transporter 2 inhibitor, has demonstrated improved glycemic control relative to sitagliptin (SITA) in clinical trials, although real-world evidence among patients treated in usual clinical practice is limited. This study was conducted to evaluate change in HbA1c among patients with T2DM receiving treatment for CANA vs. SITA. Data were from a large U.S. insurance claims database and included commercial and Medicare Advantage (MA) members with evidence of T2DM and use of SITA or CANA between 01 April 2013 and 31 December 2013. Cohorts were chosen hierarchically in the order of market entry to maximize sample sizes: the first prescription (Rx) fill for CANA was identified as the index date; then the first Rx fill for SITA was identified and index date set. Patients were age ≥18, with 6 months continuous health plan enrollment before the index date (baseline) and 9 months after (follow-up), and no claims for the index drug in baseline; those with evidence of T1DM were excluded. Patients were matched 1:1 using propensity score matching. The SITA cohort (N=12,153) was older than the CANA (N=3,993) cohort (62.4 vs. 55.3 years), was comprised of more females (45.5% vs. 41.1%) and MA members (47.9% vs. 10.5%), had greater mean baseline comorbidity (DCSI 1.1 vs. 0.8), and had fewer baseline AHAs (1.2 vs. 2.2); all p<0.001. After matching (N=1,472 each) patients were well balanced on baseline characteristics. CANA patients had greater HbA1c change between baseline and follow-up (-0.93% vs.-0.57%; p=0.004). In the subset of matched patients with baseline HbA1c ≥7, HbA1c change was also greater for CANA (-1.08% vs.-0.71%; p=0.010). In a matched pairs analysis of patients receiving care in real-world clinical practice, patients receiving CANA had a greater reduction in HbA1c.

1225-P

Overuse and Underuse of Aspirin for Primary Prevention

JOANN M. SPERL-HILLEN, PATRICK J. O'CONNOR, KAREN L. MARGOLIS, A.L. CRAIN, HEIDI L. EKSTROM, *Minneapolis, MN*

The U.S. Preventive Services Task Force (USPSTF) recommends aspirin for primary prevention of atherosclerotic vascular disease (ASCVD) when the ASCVD benefit outweighs the risk of gastrointestinal hemorrhage. The complexity and time required to assess aspirin risks and benefits can result in overuse and underuse of aspirin. As part of an NIH-funded study to lower ASCVD risk, we implemented electronic clinical decision support (CDS) algorithms to guide aspirin use based on USPSTF criteria and major bleeding risks. Baseline data was collected for whether aspirin was algorithmically recommended for all patients at their first eligible primary care encounter in 20 clinics over 2012-2014. The analysis excluded patients with CHD and included 6651 adults with diabetes (mean age 55.6, mean 10-year ASCVD risk 27.8%) and 11,682 adults meeting pre-specified criteria for high ASCVD risk without diabetes (mean age 58.4, mean 10-year ASCVD risk 24.7%). Overuse and underuse was determined by comparing concordance with (a) aspirin recommendations and (b) documented aspirin use. The CDS recommended aspirin for 4,139 (63.1%) patients with diabetes and 8,722 (74.7%) without diabetes. Among patients with aspirin recommended, aspirin was not used in 829/4139 (20%) with diabetes and 6493/8722 (74.4%) without diabetes (underuse). Among patients for whom the CDS did not recommend aspirin, aspirin was used in 1448/2969 (59.8%) with diabetes and 1021/2960 (34.4%) without diabetes (overuse). Those with diabetes who were likely to benefit from aspirin use had higher aspirin use rates (less underuse) than similar high CV risk patients without diabetes. However, those with diabetes who were unlikely to benefit from aspirin based on USPSTF criteria and bleeding risks also had higher aspirin use rates (more overuse) than patients without diabetes. Strategies to ensure greater evidence-based use of aspirin, such as providing electronic clinical decision support, may help providers more accurately assess individualized risks and benefits of aspirin.

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1226-P

Diabetes Prevention Program: Systematic Review on the Cost-Effectiveness

JOAO DIOGO DA ROCHA FERNANDES, MARIA H. HEGELUND, KATHERINE OGURTSOVA, DAVID CAVAN, LYDIA E. MAKAROFF, *Brussels, Belgium*

In 2015, the IDF Diabetes Atlas estimated diabetes was responsible for USD 673 billion in health expenditure; this represents 12% of the total expenditure on health.

ADA-Supported Research Moderated Poster Discussion

For author disclosure information, see page A696.

In this study, a systematic review on the cost-effectiveness of therapies and programs for primary prevention of type 2 diabetes and gestational diabetes was conducted.

These review included studies conducted since 2005, based on the scientific databases: Cochrane, Embase, and Medline. Initially, 2,208 results were identified as potentially relevant. After five rounds of study selection based on study quality and subject relevance, 50 articles were included in the final study. Studies were categorised by country of origin, methodology used, type of intervention, and target group. Furthermore, interventions were classified as non-cost effective, cost-effective, and cost-saving based on the willingness-to-pay thresholds set by the respective countries.

Most studies were conducted in high-income countries (n=48), with U.S. having the largest number of studies conducted (n=19). Two studies were conducted in middle-income countries (India, and Thailand). 46 studies were on type 2 diabetes, while 4 studies were on gestational diabetes.

Regarding the type of intervention, 22 studies focused exclusively on lifestyle interventions, 17 studies were on different screening programs, from which 8 were followed by lifestyle intervention, and 11 of studies examined medication only or combined with lifestyle change. Respecting to the target group, most of the studies were conducted on high risk populations (n=23), or the general population (n=14).

Out of the 50 studies included in this review, 31 studies were either cost-saving or cost-effective, 3 studies were not cost-effective, and 10 studies were either inconclusive or data provided was insufficient.

The results of this study confirm that there are many examples of lifestyle interventions, both with or without medication, that offer good value for money regarding diabetes primary prevention.

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1227-P

Healthcare Resource Use and Associated Costs for Type 2 Diabetes Patients Prescribed Sulfonylureas

BERHANU ALEMAYEHU, SWAPNIL RAJPATHAK, JINAN LIU, SAMUEL S. ENGEL, *North Wales, PA*

Sulfonylureas (SU) are commonly used generic medications in type 2 diabetes. While the overall drug costs are low, its use may be associated with additional healthcare utilization given the increased risk of hypo on SUs. The objective of this study is to evaluate overall and diabetes related healthcare resource utilization (HCRU) and associated costs in type 2 diabetes mellitus (T2DM) patients (PTS) on SU and factors associated with these outcomes. In this retrospective cohort study, T2DM PTS were identified from a U.S. healthcare claims database (MarketScan©). Included were PTS ≥18 years old on SU as monotherapy or as add-on to Metformin (MET) between 01/01/2012 to 12/31/2012 (index date) and who were continuously enrolled in a health plan one year prior and after the index date. The primary outcomes were annual total all-cause and T2DM-related HCRU and costs. Of 113,743 eligible PTS (56.8% male, average age 62.6 years), 61.6% were on SU/MET dual therapy and 38.4% were on SU monotherapy. Important factors associated with HCRU included hypoglycemia, macro/micro vascular complications, Charlson Comorbidity Index (CCI), therapy type (mono or dual) and diabetes related comorbidities. Adjusted for baseline characteristics, PTS on SU mono-therapy were more likely to use ER services (OR =1.15, 95% CI: 1.12, 1.19) and have inpatient admissions (OR=1.17, 95% CI: 1.13, 1.22), and had more frequent physician office visits (10.7 vs. 10.4 visits, p <0.01). The adjusted annual total medical cost was significantly higher for the SU monotherapy group as well ($12615 vs. $11196, P< 0.001). Prescription drug expenditures were lower for the SU monotherapy group ($2401 vs. $2691, P < 0.001). Similar patterns were observed for diabetes related ER, inpatient, physician services and prescription drug utilization and costs. This study demonstrated the high cost of care for diabetes patients treated with SU either in monotherapy or in combination with Metformin.

1228-P

Modelling HbA1c Trajectory in Patients with Type 2 Diabetes Mellitus (T2DM)

PHIL MCEWAN, JONATHAN FELLOWS, RHIANNON YAPP, KLAS BERGENHEIM, LEI QIN, NEBIBE VAROL, HAYLEY BENNETT, JASON GORDON, *Cardiff, United Kingdom, Gothenburg, Sweden, Gaithersburg, MD, Cambridge, United Kingdom*

Time-dependent trajectory of HbA1c is routinely modelled in T2DM economic evaluations, typically informed by data from the UK Prospective Diabetes Study (UKPDS). As HbA1c is related to both diabetes complication risk and time to therapy escalation, it is a critical factor in predicting health and economic outcomes. The study objective was to retrieve relevant data from the literature to inform the derivation of alternative approaches to model HbA1c trajectory.

A systematic literature review was conducted to identify studies (duration > 2 years; date range: January 2005-December 2015) that reported change in HbA1c; 68 articles were reviewed and the mean (SD) baseline characteristics of subjects were calculated: age 59.7 (5.4) years, duration of diabetes 11.1 (1) years, baseline HbA1c 8.3% (1.1%), follow up 4.1 (4.5) years, with 46% female.

Two alternative approaches to modelling HbA1c change were evaluated and contrasted with UKPDS: i) a mathematical model [MM] related to baseline, minimum and maximum observed HbA1c levels; ii) a multiple linear regression model [LM]. All analyses were undertaken using R in the Cardiff Diabetes Model. The MM equation was fitted to baseline HbA1c (8.3%), initial change in HbA1c (-0.62%) and upper quartile of maximum observed HbA1c (9.3%). The LM approach resulted in the following equation: HbA1c = 4.52+ 0.62 × Baseline HbA1c + 0.04 × Duration diabetes – 0.04 × age at baseline – 0.49 × Insulin (all parameters p<0.001). As a result, the predicted time for HbA1c to increase from 7.5% to 8.5% was 3 years (UKPDS), 4 years (MM) and 14 years (LM); the 40-year cumulative incidence of vascular complications predicted was 0.57 (UKPDS), 0.56 (MM), and 0.48 (LM).

The significant differences in HbA1c trajectories predicted across methods reflect the underlying heterogeneity of reported data and varying study designs identified in the review. This is noteworthy given the importance of HbA1c change within health economic modelling, particularly in relation to the timing of therapy escalation.

1229-P

Factors Affecting Length of Consultation Time in Diabetes Practice

YUSUKE KABEYA, JUNKO UCHIDA, YOICHI OIKAWA, AKIRA SHIMADA, YOSHIHITO ATSUMI, *Tokyo, Japan, Saitama, Japan*

Sufficient consultation time is important for establishing a doctor-patient relationship. However, the topic has been rarely investigated in diabetes practice. We examined factors associated with the length of consultation time.

This was a cross-sectional study performed at one hospital in Japan. Regular diabetes consultation of 1,199 patients with 22 doctors were investigated. Consultation time and clinical characteristics were obtained from electronic medical records. Treatment satisfaction was assessed using the diabetes treatment satisfaction questionnaire. As consultation time was right skewed, log-transformation was performed. A log-linear regression model, which included age, patient's sex, doctor's sex, type of diabetes, BMI, HbA1c, use of oral medications, use of insulin injections, use of hypnotics/anxiolytics, and satisfaction scores, was constructed to examine the association of consultation time with the variables.

Of the 1,199 patients (mean age, 66; men, 75%; type 1 diabetes, 10%), median consultation time was 9 minutes. Longer consultation time was observed in women, and patients with type 1 diabetes, higher BMI, higher HbA1c, use of insulin injections, and use of hypnotics/anxiolytics.

The results might be useful for finding patients who need more careful consultation. It is of note that no significant association with treatment satisfaction was observed. Further study for this topic is required.

Table. Variables Associated with Consultaion Time (Results of Log-linear Regression Analysis).

Variables	Ratio of consultation time	95% confidence interval
Patient's sex, women vs. men	1.08	1.01-1.15
Doctor's sex, women vs. men	1.34	1.26-1.43
Type of diabetes, T2DM vs. T1DM	0.77	0.69-0.86
BMI, increase of 1 unit	1.01	1.00-1.02
HbA1c, increase of 1%	1.06	1.03-1.09
Use of insulin injections, Yes vs. No	1.22	1.14-1.30
Use of hypnotics/anxiolytics, Yes vs. No	1.13	1.00-1.27

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1230-P

Quantifying the Health Economic Value Associated with Levels of Glycemic Control, Weight Change, and Hypoglycemia in Type 1 Diabetes Mellitus

PHIL MCEWAN, HAYLEY BENNETT, JENNIFER PRIAULX, KLAS BERGENHEIM, *Cardiff, United Kingdom, Cambridge, United Kingdom, Mölndal, Sweden*

Therapeutic guidelines advocate the use of patient-optimised management strategies and individualised targets for the management of type 1 diabetes mellitus (T1DM). Therapy-related consequences of treatment, such as weight gain and hypoglycaemia are known to act as a potential barrier to attaining optimal glycaemic control. We therefore sought to ascertain

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the respective contribution of hypoglycaemia, weight change and improved blood glucose control on predicted life expectancy and quality-adjusted life years (QALYs) in T1DM subjects.

This study used the Cardiff T1DM model with microvascular disease progression rates derived from DCCT and EDIC and cardiovascular event rates from the Swedish National Diabetes Registry to predict outcomes associated with various ages, levels of glucose control, weight and rates of hypoglycaemia.

Mean life expectancy predicted was 63.6 years. Achieving and maintaining a 1% reduction in HbA1c was associated with an estimated gain of 1.37 QALYs per patient. Changes in weight (± 3kg) and hypoglycaemia frequency (± 30%) produced a combined QALY gain of ± 0.59 (70% attributable to weight change). HbA1c reductions resulted in larger QALY benefits among younger patients with high baseline HbA1c; for a 30-year old patient, 1.48 QALYs were gained for 9% vs. 10% HbA1c, and 0.99 QALYs were gained for 7% vs. 6% HbA1c. For a 50-year old 1.01 QALYs were gained for 9% vs. 10% HbA1c, and 0.61 QALYs were gained for 7% vs. 6% HbA1c.

This analysis quantifies the QALY improvements associated improved glycaemia control in subjects with T1DM, and highlights that the beneficial effects of improved glycaemic control on QALYs may be partially offset by characteristic treatment-specific adverse effects, such as weight gain and hypoglycaemia.

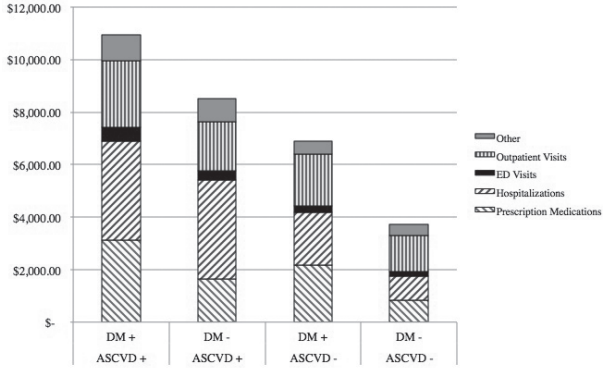
1231-P

Diabetes Mellitus Equivalent to Atherosclerotic Cardiovascular Disease from Health-Care Cost Perspective: Insights from Medical Expenditure Panel Survey

JAVIER VALERO-ELIZONDO, JOSEPH A. SALAMI, JAMAL S. RANA, OLUSEYE OGUNMOROTI, CHUKWUEMEKA U. OSONDU, ERICA S. SPATZ, SALIM S. VIRANI, RON BLANKSTEIN, MICHAEL J. BLAHA, EMIR VELEDAR, KHURRAM NASIR, *Miami, FL, Oakland, CA, New Haven, CT, Houston, TX, Boston, MA, Baltimore, MD*

The presence of DM has been considered as a risk factor equivalent to Atherosclerotic Cardiovascular Disease (ASCVD). In this study we evaluated their relative impact on direct health care expenditures utilizing the 2012 Medical Expenditure Panel Survey (MEPS). Direct costs were calculated for all-cause health care resource utilization. Variables of interest included ASCVD (coronary artery disease, stroke, peripheral artery disease), and DM diagnoses, ascertained by ICD9 codes. Two-part econometric models were utilized to study cost data; a generalized linear model with gamma distribution and link log was used to assess expenditures. Among 27,288 sampled MEPS participants (47 ± 17 years, 48% male), 8.5% had DM but no ASCVD, 3.7% had ASCVD but no DM, and 2.3% had both, which translate to 19.7, 8.6 and 5.3 million U.S. adults, respectively. The Figure highlights average healthcare expenditure by DM and ASCVD status. After accounting for covariates, incremental annual healthcare expenditure for DM alone was $3202 (95% CI 2458-3945); ASCVD alone $4760 (95% CI 2933-7224) and DM+ASCVD $7324 (95% CI 5657-8990), compared to absence of either one. Annual medical expenditures among those with DM alone were much lower compared to those with ASCVD alone. In terms of economic burden, presence of DM alone does not translate into an ASCVD economic burden equivalent.

Figure. Average Healthcare Expenditures by DM and ASCVD Status.



Abbreviations: DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; ED, emergency department
Adjusted for age, sex, family income, race/ethnicity, insurance type, geographical region, Modified Charlson Comorbidity Index* and cardiovascular risk factors (hypertension, lack of physical activity, obesity, smoking and hypercholesterolemia).
* Charlson Comorbidity Index without Cardiovascular components.

1232-P

Impact of Diabetes Treatment-Related Attributes on Costs of Type 2 Diabetes (T2DM) Patients in a Real-World Population

YI-CHIEN LEE, JIE MENG, ROMAN CASCIANO, ALLISON PERRIN, DMITRY GULTYAEV, LIYUE TONG, BRICE KITIO-DSCHASSI, *New York, NY, Loerrach, Germany, Bridgewater, NJ, Chilly Mazarin, France*

The aim of this study was to estimate the impact of diabetes treatment-related attributes on the costs for T2DM patients.

An observational, retrospective study was conducted using the Optum Clinformatics™ Database, which links medical and pharmacy claims to laboratory results. Patients ≥18 years old with T2DM, ≥1 antidiabetic medication claim, ≥1 HbA_{1c} test result, and continuous enrollment in the health plan from 1 April 2010 - 31 March 2011 were included (N=143,248). Nondiabetes specific total, inpatient, outpatient, emergency room and other costs (along with antidiabetes medication costs were defined for each patient. Generalized linear models with logarithm link were used to predict the 1-year and cumulative 3-year costs. Demographic factors and comorbidities were included as covariates in addition to the diabetes treatment-related attributes.

In the entire analysis cohort, the average 3-year cost/pt was $74,862. The percentage impact on cost of diabetes treatment-related variables is summarized in Table 1. Drug adherence was associated with lower inpatient, outpatient and emergency room costs and higher drug costs. Hypoglycemia was associated with higher costs except drug costs. Compared to HbA_{1c} values ≤7%, patients with higher levels were associated with higher total and drug costs.

Results demonstrate the positive economic impact of improved T2DM treatments.

Table 1. Impact of Diabetes Treatment-related Attributes on 3-year Cumulative Costs.[5]

		Inpatient	Outpatient	Emergency	Drug	Other[3]	Total
Average cost/Patient[1]		$32,790	$22,299	$1,290	$5,124	$13,359	$74,862
Cost driver	**Subgroup**	**Percentage Change from Reference Group[6]**					
Adherence (%)[4]	(80, 100]	-17%	-22%	-18%	429%	54%	NS[2]
	(60, 80]	-13%	-17%	-14%	249%	39%	NS[2]
	(40, 60]	-9%	-12%	-9%	130%	24%	NS[2]
	(20, 40]	-4%	-6%	-5%	52%	11%	NS[2]
	(0, 20]	Reference Group					
Hypoglycemia event	Hospitalized/ER event	49%	37%	108%	11%	26%	58%
	Non-hospitalized/ER event	24%	30%	12%	16%	17%	31%
	No hypoglycemia event	Reference Group					
HbA_{1c} level (%)	>9%	20%	NS[2]	25%	139%	-17%	20%
	(8% - 9%]	3%	NS[2]	2%	117%	-10%	10%
	(7% - 8%]	15%	NS[2]	13%	50%	-10%	9%
	(0 - 7%]	Reference Group					

1. The average costs are the mean costs derived from the study population adjusting for the follow-up period. 2. NS indicates those variables that are not significant in the model selection process at the significance level of 0.1. All other variables presented in the Table were considered significant in the model selection process at the significance level of 0.1. 3. "Other" includes the costs for which the point of service was not identified and non-antidiabetes medication costs. 4. Adherence was defined by the proportion of days covered by any antidiabetes medication. 5. Adjusted covariates include age, sex, region, comorbidity (vascular disease, chronic pulmonary disease, connective tissue disease-rheumatic disease, peptic ulcer, mild liver disease, renal disease, moderate or severe liver disease, hypertension, hyperlipidemia, obesity, gastrointestinal disease, pancreatitis, foot disease, and neuropathy), and endocrinologist visits (yes or no). 6. For outpatient, drug, other and total costs, the results of gamma model are reported. For inpatient and emergency room costs, the results of zero-inflated negative binomial model are reported.

1233-P

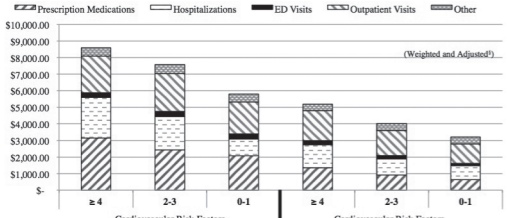
Favorable Risk Profile Associated with Lower Health Costs and Utilization among Patients With and Without Diabetes Mellitus, Free of Established Cardiovascular Disease: Medical Expenditure Panel Survey (MEPS)

JAVIER VALERO-ELIZONDO, JOSEPH A. SALAMI, JAMAL S. RANA, OLUSEYE OGUNMOROTI, CHUKWUEMEKA U. OSONDU, ERICA S. SPATZ, SALIM S. VIRANI, RON BLANKSTEIN, MICHAEL J. BLAHA, EMIR VELEDAR, KHURRAM NASIR, *Miami, FL, Oakland, CA, New Haven, CT, Houston, TX, Boston, MA, Baltimore, MD*

Patients with diabetes mellitus (DM) represent an enormous opportunity for prevention and cost reduction among those free of established cardiovascular disease (CVD). We aimed to quantify the effect of modifiable cardiovas-

cular risk factors (CRF) on healthcare expenditures and resource utilization among those with and without DM, utilizing the 2012 Medical Expenditure Panel Survey (MEPS). Variables included self-reported CRF (hypertension, hypercholesterolemia, smoking, physical activity and/or obesity) and DM, ascertained by ICD9 codes. Two-part econometric models were utilized to study cost data; a generalized linear model with gamma distribution and link log was used to assess expenditures. Among the 27,288 sampled MEPS adults without CVD (47 ± 17 years, 48% male), 52% had 0-1, 40% had 2-3, and 8% had ≥ 4 CRF, translating to 120.4, 92.6 and 18.5 million U.S. adults, respectively. Those with favorable CRF across DM status had significantly lower healthcare expenditures and resource utilization (Figure). Among patients with DM, the average medical expenditure was $2507 lower among those with 0-1 CRF vs. ≥4 CRF. In conclusion, our study provides estimates for potential healthcare savings on preventing and managing modifiable CRF among those with and without DM, free of established CVD.

Figure. Healthcare Expenditures and Resource Utilization among Non-CVD Individuals, by DM and Cardiovascular Risk Factor Status.



Prescription Medications						
Proportion with ≥ 1 purchase/refill	98%	97%	94%	88%	70%	48%
Hospitalizations						
Proportion with ≥ 1 hospitalization	13%	12%	7%	10%	6%	4%
ED Visits						
Proportion with ≥ 1 visit	22%	16%	12%	19%	13%	9%
Outpatient Visits						
Proportion with ≥ 1 visit	96%	92%	91%	84%	73%	60%

Abbreviations: CRF, cardiovascular modifiable risk factors; DM, diabetes mellitus; CVD, cardiovascular disease; ED, emergency department.
* p < 0.05, ** p < 0.01, *** p < 0.001
¶ Adjusted for CRF, age, sex, family income, race/ethnicity, insurance, region and modified Charlson Comorbidity Index (without CVD component).

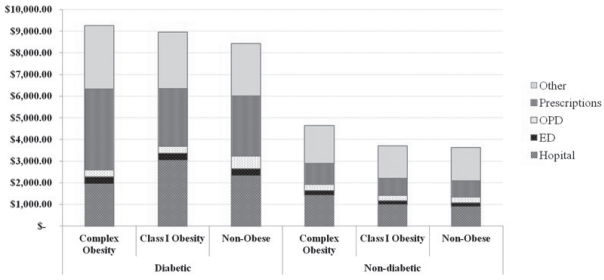
1234-P

Counting All Costs: Impact of Obesity on Health Care Expenditure among Diabetic vs. Nondiabetic Adults in the United States

JOSEPH A. SALAMI, JAVIER VALERO-ELIZONDO, CHUKWUEMEKA OSONDU, JAMAL S. RANA, ERICA S. SPATZ, EMIR VELEDAR, KHURRAM NASIR, *Miami, FL, San Francisco, CA, New Haven, CT*

The impact of obesity on healthcare expenditure among diabetic compared to nondiabetic adults in the U.S. has not been assessed recently. We used the 2013 Medical Expenditures Panel Survey (MEPS), a nationally representative survey. Non-underweight adults with diabetes mellitus (DM) [classified using ICD9 code 250] were compared to adults without DM. We calculated the incremental healthcare expenditure associated with different classes of obesity using the two-part (*probit* and *generalized linear model*) model. In 2013, the prevalence of complex obesity (body mass index [BMI] > 35kg/m^2) in the U.S. was 12.5 (28.7 million), and class 1 obesity (BMI of 30-34.5kg/m^2) was 18.7% (42.9 million), and both classes were significantly more prevalent among adults with DM (p<0.001). Healthcare expenditure adjusted for age, sex, race, and comorbidity was significantly higher among complex obese vs. nonobese adults (BMI<30kg/m^2) among nondiabetics (marginal expenditure= $1062; 95% CI: $549-$1575). There was no statistically significant marginal expenditure attributable to obesity among diabetic adults (Figure). Although obesity did not significantly influence healthcare expenditure among diabetic adults, its high prevalence and effect on nondiabetic adults make it an important epidemiologic and economic risk factor to modify in the prevention and management of diabetes.

Figure. Impact of Obesity on Healthcare Expenditure among Diabetics and Nondiabetics.



Note: "Other Expenditure" includes spending on other healthcare services such as dental care, opthalmologic care, homehealth services, etc

1235-P

Patient-Centered Outcomes and Sociodemographic Predictors of Diabetes Treatment Effectiveness

MARCIA A. TESTA, MAXWELL SU, ALEXANDER TURCHIN, DONALD C. SIMONSON, *Boston, MA*

Achieving glycemic treatment targets varies depending on clinical characteristics; however, the role of socio-demographic and patient-centered outcomes on treatment effectiveness is not as well established. We analyzed treatment effectiveness heterogeneity in T1D and T2D using pooled data from 8 randomized trials (2,927 patients, 413 clinics, 18 arms) including 12 regimens of insulin and oral agents (Metformin, sulfonylureas, thiazolidinediones) alone or in combination during 24 - 52 wks. Socio-demographics, patient-reported treatment satisfaction (71 items) and quality of life (QoL, 154 items) questionnaires were completed longitudinally. Effectiveness measures (A1c endpoint mean, and probability of endpoint A1c < 8% and < 7%) were modeled using linear and logistic regression. At baseline, subjects were 22.6% T1D (53% male, age 32 ± 14 yrs, A1c 8.0 ± 1.0%) and 77.4% T2D (58% male, age 56 ± 10 yrs, A1c 9.2 ± 1.2%, BMI 31 ± 5 kg/m^2). Endpoint A1c was 7.7 ± 1.2% with interquartile range of 6.9 - 8.3%, (p = ns for T1D vs. T2D). For T1D and T2D, 60.6% and 68.6% attained A1c < 8%, and 19.3% and 32.3% reached A1c < 7%. Regimen differences were found for all effectiveness measures (p < 0.001). Controlling for study, regimen, baseline A1c, age, BMI (all p< 0.001), and diabetes type, gender, education, income, marital status and race (all p = ns), satisfaction and QoL improvements were associated with lower endpoint A1c and higher probability of A1c < 8% and < 7% (both p < 0.01). Satisfaction associations with treatment effectiveness were due primarily to subscales of greater perceived effectiveness (p < 0.001) and lower side effects (p < 0.05). QoL associations were due to favorable changes in subscales of symptom interference, mental health, health perceptions, health ratings, side effects and symptom distress, cognitive performance, and functional health (all p < 0.02). These findings support monitoring satisfaction and QoL outcomes to achieve glycemic treatment targets and improve quality of diabetes care.

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1236-P

The Economic Benefit of Weight Maintenance and Glycemic Control in Type 2 Diabetes

GREGORY A. NICHOLS, TERESA KIMES, MAUREEN O'KEEFE-ROSETTI, KELLY F. BELL, *Portland, OR, Fort Washington, PA*

Weight loss, or weight maintenance, and glycemic control are the cornerstones of diabetes care. We compared medical costs among patients who did and did not maintain glycemic control and did or did not gain significant weight over a 4 year period.

We identified all members of Kaiser Permanente Northwest with type 2 diabetes diagnosed in 2010 or earlier who were enrolled from January 2010 through December 2013. Patients had to have at least one A1c measurement in each year and to have a body weight measurement in 2010 and 2013. Because of the association between high cost conditions (e.g., cancer) and unintentional weight loss, we focused on 6,577 patients who gained weight or lost no more than 5% and 1,577 who gained more than 5% of their 2010 weight using the 1st weight recorded in 2010 and the last recorded in 2013. We also created two categories of mean glycemic control from 2010 to 2013 (A1c <7% and ≥7%). We used calendar year 2010 to collect baseline data and compared 2013 medical costs among the four analysis groups, adjusted for demographics, comorbidities and baseline costs.

For author disclosure information, see page A696.

Over 4 years, 80% of patients maintained their weight within +/-5% of baseline and 38% had mean A1c <7%. Adjusted medical costs were significantly higher among patients who gained vs. maintained weight, regardless of glycemic control.

Our data underscore the importance of maintaining weight. Weight maintenance provided more economic benefit than glycemic control.

Table.

	A1c <7%, Weight ± 5%	A1c <7%, Weight Gain >5%	A1c ≥7%, Weight ± 5%	A1c ≥7%, Weight Gain >5%
No. of Subjects (%)	2553 (31%)	557 (7%)	4024 (49%)	1020 (13%)
Baseline Age (2010)	**58.6**	**56.3**	52.3	50.4
% Men	52.4%	**47.8%**	56.9%	**49.9%**
Baseline A1c (2010)	**6.5%**	**6.2%**	8.0%	8.2%
Baseline Weight (2010)	**210**	**205**	221	221
Adjusted 2013 Inpatient Costs	$1,763	$1,966	$2,038	$2,636
Adjusted 2013 Outpatient Costs	**$4,542**	$4,908	**$4,504**	$5,132
Adjusted 2013 Pharmacy Costs	$2,143	$2,015	$2,198	**$2,749**
Adjusted 2013 Total Costs	**$8,421**	$9,206	**$8,642**	$10,500

*Bolded cells in each row are not statistically significantly different from each other, but are statistically significantly different from unbolded cells in the same row ($p<0.01$).

Supported By: AstraZeneca

1237-P

Increased Adherence to Glucose-Lowering Agents Is Associated with Improvements in Acute Care Outcomes

KRISTINA S. BOYE, LUIS-EMILIO GARCIA-PEREZ, SARAH CURTIS, MAUREEN J. LAGE, *Indianapolis, IN, Delray Beach, FL*

The impact of diabetes acute care is significant for patients and costly to U.S. healthcare payers. Past research has generally used small populations and focused on a subset of glucose-lowering agents (GLA). This study examines the relationship between adherence to all GLA and acute care outcomes for type 2 diabetes (T2D) patients. Adherence was proxied by the proportion of days covered (PDC) and acute care (hospitalization and emergency room [ER)] outcomes included: costs, probability of visit, and number/length of visit. Data was provided by a large U.S. nationally represented database (MarketScan Commercial Claims and Encounters) from July 1, 2009 to June 30, 2014.

There were 228,074 T2D patients age 18-62 who received GLA (index date) and had continuous insurance coverage from 1 year prior through 3 years post index date. Results from multivariable analyses illustrate that as adherence improved, the probability of a hospitalization or ER visit decreased. Also, number of hospitalizations or ER visits and hospital length of stay declined. Acute care costs declined as patient adherence increased and, on average, a one point increase in adherence is associated with total acute care cost savings of $5,738,276 in this population.

Results illustrate that better T2D patient adherence are associated with improvements in acute care outcomes, suggesting benefits for both patients and health care payers.

1238-P

Socioeconomic Status and Disparities in Health Care Costs Related to Diabetes

GILLIAN L. BOOTH, GHAZAL S. FAZLI, ARLENE S. BIERMAN, LORRAINE L. LIPSCOMBE, BAIJU R. SHAH, WANRUDEE ISARANUWATCHAI, *Toronto, ON, Canada*

Low socioeconomic status (SES) is a risk factor for adverse diabetes outcomes, including avoidable hospitalizations, chronic kidney disease, cardiovascular (CV) events and premature death. In Canada, income-related gaps in CV morbidity and mortality appear greater among younger adults with diabetes (<age 65) who do not receive drug coverage as an insurable benefit. We used administrative health care databases from Ontario, Canada to study the relationship between SES and health care expenditures over a 10-year period among 606,051 adults with diabetes who were <age 65 vs. age 65+ on April 1, 2002. SES was assigned to individuals based on their neighborhood's median household income level, divided into quintiles (Q). Generalized linear regression was used to examine the effect of SES on annual health care costs (in 2014 Canadian [CAD] dollars) related to hospitalizations, outpatient and emergency room visits, same day surgeries/procedures, outpatient laboratory tests/imaging, prescription drugs, and home care. Overall, there was an inverse relationship between SES and health care expenditures, particularly among groups under age 65 - in whom yearly costs were 40% higher in Q1 vs. Q5 ($7402 vs. $5276) compared to seniors, where yearly costs were only 9% higher in Q1 vs. Q5 ($14502 vs. $13284). After adjusting for baseline age, sex, diabetes duration, prior CV events and comorbidity, total health care costs were $1876 per person per year higher among younger adults with diabetes in Q1 vs. Q5 translating to $139M more per year among all patients in the lowest SES group compared to those in Q5. In comparison, Q1 was associated with an excess cost of $1200 per person per year relative to Q5 among older adults (or $78M more per year overall). In conclusion, health care costs were higher among lower income groups with diabetes in our publicly funded health care system. However, the observed disparity in health care costs was less among older populations who receive drug coverage as a universal benefit.

Supported By: Canadian Diabetes Association

1239-P

Predictive Model for Estimating Cost of Incident Diabetes Complications

JIA ZHU, PETER KAHN, JANINE KHUDSEN, SANJEEV N. MEHTA, ROBERT A. GABBAY, *Boston, MA*

The cost of diabetes care accounts for a significant proportion of healthcare expenditures. Cost models based on updated incident complication rates and associated costs are needed to improve financial planning and quality assessment across the U.S. healthcare system. We developed a cost model using published data to estimate the direct medical costs of incident diabetes-related complications in a U.S. population of adults. A systematic literature search provided the incidence and/or cost of diabetes-related complications; 54 studies met eligibility criteria. Models estimated incident and follow-up costs for diabetes complications (cardiovascular disease, neuropathy, nephropathy, retinopathy, and acute metabolic complications) for a cohort of 10,000 adults with diabetes over 1-, 3-, and 5-year time horizons; incident rates were held constant over each time period. Estimated costs for the most costly diabetes complications are presented in the Table. This model provides a benchmark for health systems to prospectively model interventions to reduce diabetes-related medical expenditures and estimate cost-effectiveness and potential leakage within a care delivery network.

Table. Estimated Direct Costs for Incident Diabetes Complications per 10,000 Adults with Diabetes.

Diabetes Complication	1-Year Cost	3-Year Cost	5-Year Cost
Congestive Heart Failure	$7,320,287	$26,791,067	$50,697,865
Gangrene	$2,844,381	$9,426,696	$17,200,417
End Stage Renal Disease	$4,225,384	Not Available	$13,211,204
Blindness	$320,460	$1,922,758	$4,806,896

1240-P

Budget Impact in the United States with Insulin Degludec Compared with Insulin Glargine

JAMES WEATHERALL, LISA BLOUDEK, *Plainsboro, NJ, Palm Harbor, FL*

Insulin degludec (IDeg) is a newly approved once-daily long-acting basal insulin indicated to improve glycemic control in adults with diabetes mellitus (DM). A 1-year budget impact model was developed to evaluate costs of IDeg vs. insulin glargine (IGlar) through a simulation for a potential United States (U.S.) health plan population of 35 million and for the entire U.S. population. Type 1 DM patients on basal-bolus therapy (T1DMBBT), type 2 DM patients on basal-oral therapy (T2DMBOT), and type 2 DM patients on basal-bolus therapy (T2DMBBT) were considered. The goal was to quantify the annual budget impact if all patients switched from IGlar to IDeg. The analysis captured direct medical costs associated with insulin treatment and costs related to managing hypoglycemic episodes. It was estimated that there were a total of 59,780 T1DMBBT, 383,145 T2DMBOT, and 171,325 T2DMBBT patients expected to use long-acting insulin for the health plan analysis. For the whole U.S., the patient totals were 534,439, 3,425,352, and 1,531,662, respectively. For the health plan analysis, IDeg demonstrated cost savings of $240 million per year, accounting for total cost savings of 3.5% vs. IGlar. Among T1DMBBT patients, IDeg was associated with cost savings of –$0.05 per-member per-month (PMPM), driven primarily by reduced insulin utilization. IDeg was also found to be cost saving among T2DMBOT patients (–$1.10 PMPM), driven primarily by reductions in the cost of treating severe hypoglycemic episodes. However, these savings were offset by $0.58 PMPM due to an increase in cost among T2DMBBT patients. The resulting PMPM overall was –$0.57. For the whole U.S. population, scenarios adjusting for market uptake assumptions were conducted. No scenario produced a net annual budget impact increase of >$900

million. These results suggest the long-acting pharmacokinetic profile, reduced insulin utilization, and reduced rate of hypoglycemic episodes associated with IDeg may translate into reduced costs overall for payers compared to IGlar.

1241-P

Effect of a National Reimbursement Policy for Blood Glucose Test Strips on Glycemic Control and Rate of Severe Hypoglycemia in Korean Adult Patients with Type 1 Diabetes

SANG-MAN JIN, SO-YOUNG PARK, JONGHA BAEK, JI EUN JUN, SEUNG-EUN LEE, SUNGHWAN SUH, CHANG HEE JUNG, BYUNG-WAN LEE, JAE HYOUNG CHO, CHEOL-YOUNG PARK, JAE HYEON KIM, *Seoul, Republic of Korea, Jinju, Republic of Korea, Busan, Republic of Korea*

We evaluated the effect of a national reimbursement policy for blood glucose test strips on glycemic control, SMBG frequency and rate of severe hypoglycemia (SH) in Korean adult patients with type 1 diabetes mellitus (T1DM). This was a prospective cohort study of the 466 adult patients with T1DM from the five tertiary referral hospitals who registered for the reimbursement program of blood glucose strips, which has started in June 2011 by Korea National Health Insurance Service (KNHIS). During the 12-month follow-up period, SMBG frequency (times/day), rate of SH (times/month), glycated hemoglobin (HbA1c), and other glycometabolic parameters were evaluated. Mean difference from baseline in HbA1c (%) was 0.08 (95% confidence interval, -0.08 to 0.25; $P = 0.319$). Median SMBG frequency increased from 2.0 (interquartile range [IQR] 0-4.0) per day at baseline to 5.0 (IQR 4.0-6.3) per day at 6 months and 3.0 (IQR 1.0-5.3) per day at 12 months after registration ($p < 0.001$). More frequent SMBG measurement at baseline and higher rate of SH at baseline were independently associated with increased SMBG frequency over the study period. Rate of SH at 12 months (median 1.0 times/month, IQR 1.0-2.0) decreased from that at baseline (median 1.5 times/month, IQR 0-3.0; $p < 0.001$). More frequent SMBG measurement at baseline and increased SMBG frequency over the study period independently associated with decreased rate of SH. In conclusion, the reimbursement policy reduced the rate of SH upto 12 months with increased frequency of SMBG, although it did not induce a reduction in HbA1c.

1242-P

Hierarchical Medical Care Dramatically Improve the Control of Cardiovascular Risk Factors in Diabetes in China

JIANZHONG XIAO, TELEMEDCHINA STUDY GROUP, *Beijing, China*

Objective: Due to the limited resources for the delivery of standard diabetes care, more than 90% of patients with diabetes in China have not reached composite target goal of blood glucose (HbA1c<7.0%), blood pressure (<140/80 mmHg) and serum low density lipoprotein cholesterol (<2.6 mmol/l) in China. We explore an approach of hierarchical medical care to improve the situation.

Methods: Twenty centers of community clinics were randomized divided into 2 groups (10 sites, n=570), conventional care group and intervention group (11 site, n=710). Patients in the conventional group were treated as usual care in community clinics. In the intervention group, patients were managed by a hierarchical medical care model, i.e., routine care from community clinics and support from tier 2 and tier 3 hospitals. The Chinese Diabetes Society guideline were implemented by computerized therapeutic assistant guide, internet-based expert supervising and patient education.

Results: In the end of one-year intervention, the proportion of patients reached target goal for HbA1c, systolic blood pressure, diastolic blood pressure, LDL-c and composite of all 4 risk factors were 50.9%, 71.7%, 34.1%, 47.7 and 9.7% in the conventional group, in contrast, they were 48.8%, 86.4%, 59.7%, 56.3% and 20.3% in the intervention group (P<0.05 except for HbA1c). There were 41.7% and 69.2% taken statin in the conventional group, and 68.8% and 86.0% in the intervention group.

Conclusion: Diabetes management in community clinics can be largely improved by systemic intervention.

Supported By: Ministry of Science and Technology of the People's Republic of China

1243-P

Inpatient Costs and Utilizations among Type 1 Diabetes Patient Treated with Continuous Subcutaneous Insulin Infusion vs. Multiple Daily Injections

JANICE K. CHUNG, CYRUS ZHU, MAX S. GILL, *Northridge, CA*

Diabetes often leads to frequent inpatient utilizations and high healthcare costs due to uncontrolled glycemic level. This study aims to assess inpatient costs and utilizations from a payer's perspective among type 1 diabetes (T1D) patients treated with continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI). Data were extracted from Truven MarketScan® database (2008-2012). Patients were included in the analyses if they had at least 2 primary or secondary outpatient claims associated with T1D or 1 claim associated with T1D in inpatient setting. Specific algorithms were applied to define T1D patients on 2 diabetes treatment regimens (CSII vs. MDI). Patients on CSII therapy were categorized into new and existing CSII. MDI patients were identified by having claims for basal and bolus insulins using specific national drug codes (NDCs). The analyses were restricted to patients aged 18-64 under the continuous enrollment to same health plans with pharmacy benefits and continuously receiving CSII or MDI therapy from the analysis index date. Patients on continuous glucose monitoring (CGM) system during the study period were excluded from the analyses. Annual inpatient costs and utilizations were evaluated during the one-year follow-up since the study index date.

Two cohorts were matched based on patient characteristics: age, gender, Charlson comorbidity index (CCI), macrovascular and microvascular complications. Matched annual inpatient costs, adjusted to 2013 dollars showed that CSII patients had approximately 20% lower inpatient cost and MDI was associated with an increased risk for an inpatient utilization compared to CSII patients.

Higher inpatient costs were observed among T1D MDI patients in U.S. and alternative insulin intensive therapy such as CSII therapy should be considered among T1D patients trying to maintain a tight glycemic control which may reduce inpatient costs and utilizations.

1244-P

Long-Term Economic Outcomes of Empagliflozin (Jardiance) Treatment in Type 2 Diabetes Mellitus (T2DM) based on the EMPA-REG Outcome Trial

ANURAAG R. KANSAL, YING ZHENG, IRINA PROSKOROVSKY, ODETTE REIFSNIDER, PRASHANTH KANDASWAMY, ANTONIO RUFFOLO, *Bethesda, MD, Montreal, QC, Canada, Ingelheim, Germany*

Empagliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT2), is an approved treatment for management of high glucose in patients with T2DM. The effect of empagliflozin in addition to standard of care (SoC) on cardiovascular (CV) morbidity and mortality was evaluated in the EMPA REG Outcome trial. Empagliflozin was found to significantly reduce composite CV event rates (HR: 0.86; 95% CI: 0.74 - 0.99) and CV mortality (HR 0.62; 95% CI: 0.47 - 0.77) in a population of patients at high risk for CV events.

An economic model was developed to extrapolate the outcomes of empagliflozin plus SoC compared to SoC over patients' remaining lifetime. Time-dependent survival regression analysis was performed on the EMPA REG Outcomes trial data for CV death, CV events including myocardial infarction and stroke, and renal outcomes to model event rates over time and the interaction between events. The model was validated by comparing simulated and observed outcomes at 3 years. Costs for a UK setting and patient utilities were obtained from the literature. Only empagliflozin was considered for pharmacy costs. Model outcomes included total and incremental costs incurred, life years (LY), and quality-adjusted life-years (QALYs). Future costs and QALYs were discounted at a 3.5% annual rate.

Consistent with the trial data on CV mortality, empagliflozin was predicted to result in longer survival (14.0 LY vs. 12.0 LY with SoC). This was attributable to both a direct treatment effect on CV mortality and an indirect effect via reductions in other CV events, particularly heart failure hospitalization (2.0 events/100 patient-years with empagliflozin vs. 3.0 events/100 patient-years with SoC). This results in a predicted 0.9 incremental QALYs with empagliflozin at an incremental cost of £3,849 per patient and an incremental cost-effectiveness ratio of £4,206/QALY. This is well below the common threshold for cost-effectiveness in the UK (£30,000/QALY).

1245-P

Diabetes Specialty Support in Primary Care

CARLOS E. MENDEZ, SUN JUNG KANG, TABITHA HARRIS, *Milwaukee, WI, Albany, NY*

At the Albany VA Medical Center, we designed a process to provide ongoing diabetes specialty support to primary care providers (PCP) within the primary care clinics. A full time nurse practitioner (NP) and certified diabetes educator (CDE) was recruited and trained. Management recommendations were discussed with the PCP through a "hand-off" session. We hypothesized that patients directly seen by the NP, CDE would have significant improvement in A1c, LDL, and weight, and that patients not directly seen by the NP, CDE, but seen by participating PCPs would also benefit indirectly from the intervention. Data were extracted from the VISN2 Data Warehouse. All primary care patients with A1c over 7% were included in the study from November 2013 until September 2015. 217 patients established care directly with the NP, CDE (Direct), 2823 patients had no direct contact, but were patients of a participating PCP (Indirect), and 3589 patients had no contact with the process. Results

For author disclosure information, see page A696.

are shown below. A1c decreased significantly for each group. The differences in between groups were only significant in between the direct and indirect group, but not between the indirect and the no contact group. There were also weight and LDL reductions but these were not significant. Results suggest that patients seen by the NP CDE in primary care benefit from the direct intervention, while the indirect benefits on other patients seen by participating PCP's were not superior to patients with no contact.

Table. Changes in Clinical Variables.

Variables	1. Direct	2. Indirect	3. No Contact	1 vs. 2	1 vs. 3	2 vs. 3
A1c (%)	-0.58	-0.23	-0.25	0.003	0.003	0.902
Weight (Kg)	-0.37	-2.47	-2.07	0.064	0.145	0.253
LDL-C (mg/dL)	-7.17	-4.55	-2.95	0.279	0.058	0.043

1246-P

Patient Perspectives on the Daily Impacts of Diabetes Management and Unmet Needs

NANCY F. LIU, ADAM S. BROWN, PHIN YOUNGE, MARK YARCHOAN, RICHARD S. WOOD, KELLY L. CLOSE, *San Francisco, CA, Baltimore, MD*

Despite improvements in therapies and devices for the treatment of diabetes, the psychosocial burden of living with the disease remains high for patients. To better understand the impacts of diabetes on daily life, we created an online survey as part of an FDA-patient dialogue on the unmet needs in diabetes, which received a total of 7,458 responses from patients with diabetes and their caregivers.

In our sample, only 37% of type 1 and 54% of type 2 respondents met the ADA goals of an A1c ≤7.0%, despite extensive use of diabetes technology in type 1 respondents (71% on pumps, 46% on CGM) and the use of insulin in type 2 survey respondents (48%). A majority of patients with type 1 and type 2 reported that diabetes had a negative impact on their life when planning for the future (72% and 54%, respectively), while most patients with type 1 also reported negative impacts on their ability to take on life's challenges (67%), their self-confidence (66%), and their success at work or school (67%). Respondents also ranked the five biggest barriers to diabetes management (see Table), which reflected the high levels of stress, cost, and therapy burden associated with managing diabetes every day.

These data highlight the significant impact patients face from living with diabetes and areas where new devices and therapies may address current unmet needs in diabetes management.

Table.

	Type 1 % of n=14,095 total mentions	Type 2 % of n=3,366 total mentions
#1 Most Frequently Mentioned Barrier	Cost of medications and devices and care (24%)	Difficulty sticking to diet and exercise (23%)
#2 Most Frequently Mentioned Barrier	Stress involved in managing diabetes (24%)	Cost of medications and devices and care (18%)
#3 Most Frequently Mentioned Barrier	Side effects from diabetes medications, such as hypoglycemia and weight gain (14%)	Stress involved in managing diabetes (15%)
#4 Most Frequently Mentioned Barrier	Difficulty sticking to diet and exercise (8%)	Side effects from diabetes medications, such as hypoglycemia and weight gain (13%)
#5 Most Frequently Mentioned Barrier	Managing the numbers of pills/insulin doses you have to take each day (7%)	Managing the numbers of pills/insulin doses you have to take each day (6%)

1247-P

Retrospective Study of the Association between Adherence to Glucagon-like Peptide-1 Receptor Agonist Therapy and Hospitalization Risk and Costs

HIEP NGUYEN, KATHERINE CAPPELL, JAMES NELSON, BONG-CHUL CHU, STEPHEN JOHNSTON, *Fort Washington, PA, Ann Arbor, MI, Bethesda, MD*

The associations between adherence or non-adherence to glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy and hospitalization risk/costs are unknown. This retrospective cohort study used a U.S. administrative claims database to examine these associations in U.S. patients with type 2 diabetes (T2D). Adult patients with T2D were included if they were GLP-1RA-naïve, initiated GLP-1RA therapy from 2/1/2012-10/1/2012 (date of initiation=index), and had continuous enrollment for 12 months before (baseline) to 12 months after index (follow-up). The proportion of days covered (PDC), a database measure of adherence, for the initiated GLP-1RA was calculated over follow-up and dichotomized into adherent (≥80% PDC) and non-adherent (<80% PDC). Study outcomes were overall and diabetes-specific hospitalization and associated costs. Multivariable regressions compared outcomes between adherent and non-adherent patients, adjusting for confounders. Study sample included 17,275 patients; 5,305 (30.7%) adherent and 11,970 (69.3%) non-adherent. In adjusted analyses, compared with non-adherent patients, adherent patients had statistically significant lower hospitalization risk and costs (Table). In real-world U.S. clinical practice, non-adherence with GLP-1RA therapy was strongly associated with increased hospitalization risk and costs.

Table.

Hospitalization Type	Multivariable-Adjusted Association between Adherence (≥80% PDC for GLP-1RA therapy) and Hospitalization Risk and Costs	Result
Overall	OR of hospitalization	OR=0.56, *P*<0.001 (non-adherent = reference)
	Probability of hospitalization	5.6% adherent vs. 9.4% non-adherent, *P*<0.001
	Hospitalization cost difference*	$1,675 lower for adherent vs. non-adherent patients, *P*<0.001
Diabetes-specific	OR of hospitalization	OR=0.55, *P*<0.001 (non-adherent = reference)
	Probability of hospitalization	3.8% adherent vs. 6.6% non-adherent, *P*<0.001
	Hospitalization cost difference*	$710 lower for adherent vs. non-adherent patients, *P*<0.001

GLP-1RA = glucagon-like peptide-1 receptor agonist; OR=odds ratio; PDC=proportion of days covered.*In overall population N = 17,275 (i.e., not restricted to those with at least one hospitalization).

Supported By: AstraZeneca

1248-P

Time Until Insulin Initiation for Canagliflozin (CANA) vs. Sitagliptin (SITA) in Dual Therapy and Triple Therapy for Type 2 Diabetes Mellitus (T2DM) in the UK

MELANIE SCHROEDER, EDMOND CHAN, MICHAEL WILLIS, PIERRE JOHANSEN, ANDREAS NILSSON, AGATA SCHUBERT, CHERYL NESLUSAN, *High Wycombe, United Kingdom, Lund, Sweden, Warsaw, Poland, Raritan, NJ*

Insulin therapy is associated with weight gain, hypoglycemia, and for some patients needle anxiety, and many patients and physicians prefer to delay insulin therapy as long as possible. CANA, a sodium glucose co-transporter 2 inhibitor, provides HbA1c and blood pressure lowering, along with weight loss and a low intrinsic risk for hypoglycemia. Because CANA has better HbA1c lowering than SITA, CANA may postpone the need for insulin and improve patient outcomes. This analysis estimated time to insulin initiation for CANA vs. SITA in dual and triple therapy in the UK healthcare setting using economic modeling techniques. The validated Economic and Health Outcomes Model of T2DM was used to simulate mean time to insulin over 40 years, separately by treatment arm. Population characteristics, treatment effects, and adverse event rates were sourced from CANA trials for both arms. Per the label, CANA was initiated at 100 mg and increased to 300 mg as needed to maintain glycemic control. Insulin rescue therapy consisted of basal insulin initiated when HbA1c first exceeded 7.5% or when CANA was discontinued because eGFR declined below values per the label, followed by addition of prandial insulin as needed to maintain continued glycemic control. Insulin treatment effects and hypoglycemic event rates were sourced from the literature. Treatment with both CANA and SITA were maintained as insulin was initiated. CANA delayed mean time until insulin therapy by 0.9 years in dual therapy (5.7 vs. 4.8 years) and by 1.2 years in triple therapy (5.1 vs. 3.9 years). Corresponding in part to these delays in starting insulin were fewer severe hypoglycemic events (0.016 vs. 0.017 per patient-year in dual therapy and 0.048 vs. 0.057 per patient-year in triple therapy) and improved weight profiles. Simulation results suggest that CANA may be associated with meaningful delays in starting insulin therapy vs. SITA in both dual and triple therapy in the UK.

Supported By: Janssen-Cilag Ltd

1249-P

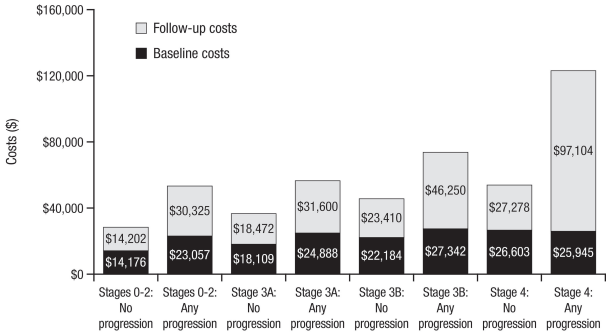
Evaluation of the Progression of Chronic Kidney Disease (CKD) and Associated Costs in U.S. Patients with Type 2 Diabetes Mellitus (T2DM)

CHERYL NESLUSAN, LESLIE MONTEJANO, DUNCAN O'BRIEN, ROBERT CUDDIHY, *Raritan, NJ, Cambridge, MA*

This retrospective study examined CKD progression and associated costs in 72,686 U.S. adults with T2DM based on claims and electronic medical record data from the 2005 through 2013 MarketScan Databases. At base-

line, 82.2%, 10.7%, 5.4%, and 1.6% of patients were classified as Stages 0-2, 3A, 3B, or 4 CKD. Kaplan-Meier estimates showed that 21.2%, 48.2%, 47.2%, and 61.2% of patients in Stages 0-2, 3A, 3B and 4 CKD progressed to a higher stage during follow-up. Mean annualized costs increased with CKD severity; the greatest cost differences were found for patients in Stage 3B and 4 CKD who progressed to a higher stage (Figure). Among patients who progressed, annualized costs increased and were 61% ($16,021), 56% ($14,789), 84% ($25,186), and 468% ($131,386) higher for those starting in Stages 0-2, 3A, 3B, and 4 CKD. Multivariate regression, which adjusted for patient demographic characteristics and comorbidities, indicated that there was no statistical difference in baseline and follow-up costs for those in Stages 0-2 vs. 3A CKD, but incremental costs (95% confidence interval) were $6,008 ($1,814-$10,203) and $11,889 ($3,449-$20,329) higher for patients in Stage 3A vs. 3B CKD and Stage 3B vs. 4 CKD, respectively. These findings illustrate that CKD progression is a driver of medical costs in patients with T2DM; early treatment intervention may be beneficial to offset this cost burden.

Figure. Mean Annualized Incremental Health Care Costs at Baseline and Follow-up by CKD Progression Status (Unadjusted).*



*Mean follow-up costs were calculated as per person per year given the variable length of follow-up in this period. Mean follow-up time was 29.6 months (standard deviation 21.8). The baseline period was 12 months for all patients.

Supported By: Janssen Global Services, LLC

1250-P

Virtual Endocrinologist: Hospital Diabetes Management via Telemedicine

MARK KIPNES, STEVEN HAFFNER, TERESA LIGHTNER, RAJESH GARG, FIRAS AKHRASS, VIJAYVEER S. PAMAR, AMNA SALHIN, JACOB VADAKEKALAM, JAVIER D. PENA, CYNTHIA L. KIRKLAND, MERRI PENDERGRASS, *San Antonio, TX, Shavano Park, TX, Harlingen, TX, Boston, MA, Tucson, AZ*

Many hospitals in remote areas lack an endocrinology consult service. We performed a study to evaluate whether inpatient glucose management by telemedicine was safe and effective. Patients hospitalized in a medically underserved area in Texas were randomized to receive care by endocrinologists via telemedicine (TELE; N=29) or non-endocrinologists by usual care (UC; N=28). Patients in the TELE group were treated with basal bolus therapy unless clinical circumstances dictated otherwise. The UC group received all care, including insulin management, from their hospitalist team. Point-of-care blood glucose (BG) readings were obtained pre-meal, bedtime and occasionally at 0300. BG readings obtained within one hour of previous readings were excluded to avoid ascertainment bias. Hospital day one readings were also excluded.

Results are shown in the Table. The TELE group had significantly more BGs in the target range, fewer BGs in the higher than target range, and no differences in hypoglycemia as compared to the UC group.

Conclusion: Endocrinology care via telemedicine is feasible in hospitals that lack an endocrinology consult service. This intervention improves glycemic control in hospitalized patients. Further large trials will be necessary to evaluate other health outcomes and cost-effectiveness.

Table.

	TELE	UC	P value
Age, mean +/-SD, (years)	62 +/- 14	59 +/- 11	NS
Female Sex (N, %)	11 (38)	11 (39)	NS
Mean daily BG, mg/dL (up to 14 days)	166.61	202.94	P <0.001
Overall BGs in 70 - 180 range (N, %)	514/812 (63%)	265/617 (43%)	P <0.001
BGs in 70 - 180 range per patient (%)	62%	38.4%	P <0.001
BGs > 250 (N, %)	90/812 (11)	142/617 (23)	P <0.001
BGs < 70 (N, %)	26/812 (3.2)	17/617 (2.8)	0.24

1251-P

Characterizing the Health Economic Benefit of Key Therapeutic Outcomes in the Management of Type 2 Diabetes

PHIL MCEWAN, VOLKER FOOS, MARK LAMOTTE, MARC EVANS, *Cardiff, United Kingdom, Vilvoorde, Belgium*

Therapeutic guidelines advocate individualised care for type 2 diabetes (T2D). The health economics of T2D is primarily driven by glycaemic control, hypoglycaemia and BMI. This study presents the economic value (cost savings and quality-adjusted life expectancy [QALE] gains) for a range of plausible clinical outcomes in T2DM.

The published and validated IMS Core Diabetes Model (CDM) was used to explore the discounted costs of complications and QALE gains associated with a range of ages, varying the following baseline profile: HbA1c 8.5%, BMI 33kg/m2, 1 severe hypoglycaemic event (SHE)/year and 12 non-severe hypoglycaemic events (NSHE)/year. Multiple linear regression equations were fitted to model outputs using R 3.2.2.

Total costs and QALEs were characterised by the following equations: costs = -137775 + 2064 x age + 30668 x HbA1c – 417 x (age x HbA1c); QALE = 26.236 - 0.203 x age -0.0644 x BMI-0.0154 x NSHE -0.51 x SHE -0.68 x HbA1c+0.00359 x (age x HbA1c). Changes in QALE by age are given in the Table. A 1% reduction in HbA1c resulted in cost savings of £13,991, £9.821, £5652 and £1,483 for subjects aged 40, 50, 60 and 70 years, respectively.

Treatment strategies that achieve reductions in HbA1c and hypoglycaemia provide the greatest economic value, with BMI impacting to a lesser extent. Whereas the impact of HbA1c is substantial in younger patients, the effects of other parameters are not age-related.

Table. Change in QALE Associated with Reductions in HbA1c, BMI and Hypoglycaemia.

Age	1% HbA1c reduction	1% HbA1c + 1 BMI reduction	1% HbA1c + 1 unit BMI reduction + no NSHE	1% HbA1c + 1 unit BMI reduction + no NSHE + no SHE
40	0.5364	0.6008	0.7856	1.2956
50	0.5005	0.5649	0.7497	1.2597
60	0.4646	0.529	0.7138	1.2238
70	0.4287	0.4931	0.6799	1.1879

1252-P

Eliciting Patient Treatment Preferences Using a Clinical Decision Support System

PATRICK J. O'CONNOR, JOANN M. SPERL-HILLEN, LAUREN A. CRAIN, HEIDI L. EKSTROM, KAREN L. MARGOLIS, *Minneapolis, MN*

CV Wizard is a web-based EHR-integrated point-of-care clinical decision support (CDS) system that presents personalized cardiovascular (CV) risk information to primary care providers (PCP) and patients in both a low numeracy and high numeracy format. Here we report PCP perspectives on how this CDS system affected shared decision making and patient-centered care. Twenty clinics were randomized to either usual care (UC) or use of the CDS system with diabetes or high reversible cardiovascular risk adults. The CDS system targeted 20% of office visits, and was used at 70-80% of targeted visits over a 2-year period. Consented providers (n=102) were surveyed at baseline and 18 months after implementation. Corrected survey response rates were 90% at baseline and 82% at follow-up. Generalized linear mixed models were used to compare UC and CDS responses to common questions at baseline and follow-up, and CDS users were queried on their perceptions of the CDS system at follow-up only. Compared to UC, PCPs in the CDS group reported increased follow-up rates of CV risk calculations while seeing patients (73% vs. 28%, p=.006), being better prepared to discuss CV risk reduction priorities with patients (98% vs. 78%, p=.03), providing accurate advice on aspirin for primary prevention (75% vs. 48%, p=.02), and more often discussing CV risk reduction (60% vs. 30%, p=.06). PCP users reported that the CDS system improved CV risk factor control (98%), saved time talking to patients about CV risk reduction (93%), efficiently elicited patient treatment preferences (90%), was useful for shared decision making (95%), influenced treatment recommendations (89%), and helped initiate CV risk discussions (94%); 85% of PCPs reported that their patients liked CV Wizard. The CV Wizard CDS system was successfully integrated into the workflow of primary care visits with high sustained use rates, high PCP satisfaction, high patient satisfaction, and positive impacts on shared decision making and patient-centered care.

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For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

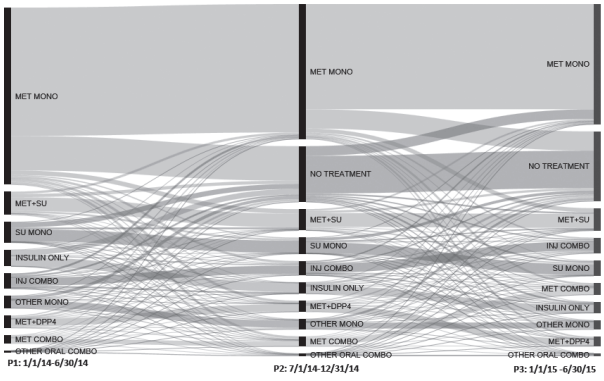
1253-P

Treatment Patterns in Patients Initiating Antihyperglycemic Treatment for T2DM in a U.S. Managed Care Plan

ERIN K. BUYSMAN, SARAH W. THAYER, STEPHANIE A. KORRER, MARY J. KVANBECK, LAURA K. BECKER, *Eden Prairie, MN, San Francisco, CA*

This study evaluated patterns of initial antihyperglycemic agent (AHA) treatment (Tx) in patients with type 2 diabetes mellitus (T2DM) in a managed care plan and examined Tx changes over time. The sample included 29,123 patients age ≥ 18 with T2DM enrolled in a commercial or Medicare Advantage health plan from 7/1/13 through 6/30/15, who began AHA Tx during P1 (Figure). Tx patterns were also evaluated in P2 and P3. Patients with T2DM who began AHA Tx had an average age of 60 years with mean A1c of 7.09% in the 6 months prior to P1; 53.5% were male. Approximately 61% of patients initiated Tx with Metformin monotherapy (MET MONO), 15% with MET + other oral combinations, 12% with sulfonylurea or other MONO and 11% with insulin only or injectables combined with other medications. Nearly 50% of patients remained on their initial Tx regimen through the end of the study period; 19% of patients had no Tx in P2 and 24% in P3. Most MET MONO initiators (57%) continued with MET MONO through P3; 29% of patients switched or added AHA Tx. In line with current ADA guidelines, the majority of patients initiated MET-containing regimens as first-line AHA Tx. While half of patients remained on their initial Tx regimen through the end of the study period, the rate of discontinuation in patients that have initiated therapy for T2DM is high, indicating a need for further research to identify whether unmet need or gaps in diabetes education exist.

Figure. AHA Treatment Patterns among Patients with T2DM Initiating Therapy.



1254-P

Prescription Expenditures as a Proportion of Health Care Spending in Diabetes Mellitus: Insight from 2013 Medical Expenditure Panel Survey

JOSEPH A. SALAMI, JAVIER VALERO-ELIZONDO, OLUSEYE OGUNMOROTI, MICHAEL J. BLAHA, JAMAL S. RANA, ERICA S. SPATZ, EMIR VELEDAR, KHURRAM NASIR, *Miami, FL, Baltimore, MD, San Francisco, CA, New Haven, CT*

The lenient regulation of drug pricing and other market factors resulting increasing medication cost is of concern. In this study, we assess the proportion of healthcare spending on prescriptions and its association with comorbidity burden among diabetic adults aged ≥18 years in United States. Using data from the 2013 Medical Expenditure Panel Survey (MEPS), we classified diabetes using ICD9 code (250), and estimated comorbidity burden using Charlson Comorbidity Index (CCI). Generalized linear model was used to estimate the *per capita* total healthcare and pharmaceutical expenditures, and the proportion of total health care spending used on medications across CCI. About 23 million adults (mean age±SD: 61.7±23.5 years, 50% females) had DM. Overall 25% had CCI=1, 11% had CCI =2. Total healthcare expenditure among those with DM was about $285 billion, 31.9% ($91 billion) of which was spent on medications. Pharmaceutical expenditure as a proportion of total healthcare spending had no statistically significant association with CCI (Table). Pharmaceutical expenditure is a significant proportion of healthcare spending among those with established DM independent of comorbid disease burden. It is imperative to critically assess interplay of issues such as pricing and appropriate utilization to counter increasing healthcare spending in this high risk population.

Table. Per Capita and Total Expenditures Associated with Burden of Morbidity among Those with Diabetes.

	Charlson Comorbidity Index		
	0 (n=14,968,315)	1 (n=5,681,146)	2 (n=2,475,302)
Per Capita Expenditure and Proportion†			
Total health care expenditure[Δ] [95% CI]	$8857 [$7451, $10262]	$14746 [$5969, $23524]	$27988 [$2742, 53233]
Pharmaceutical expenditure [95% CI]	$3012 [$2153, $3872]	$5513 [$3512, $7512] *	$6659 [$4016, $9303] *
Pharmaceutical expenditure (per $100 of total health expenditure) [95% CI]	$46 [$41, $51]	$44 [$29, 61]	$38 [$15, 62]
Population-level Expenditure			
Total health care expenditure (Billion USD, 2012)	$133	$84	$69
Total pharmaceutical expenditure (Billion USD, 2012)	$45	$31	$17

†Mean values computed using the generalized linear model with family (gamma) and link (log). *p<0.05. ΔAll costs were reported in 2013 USD.

1255-P

The Role of Estimated Glomerular Filtration Rate (eGFR) in Cost-Effectiveness (CE) Analyses Using Canagliflozin (CANA) vs. Sulfonylurea (SU) to Treat Type 2 Diabetes Mellitus (T2DM)

CHERYL NESLUSAN, MICHAEL WILLIS, PIERRE JOHANSEN, MELANIE SCHROEDER, ANDREAS NILSSON, EDMOND CHAN, CHRISTIAN ASSEBURG, AGATA SCHUBERT, *Raritan, NJ, Lund, Sweden, High Wycombe, United Kingdom, Warsaw, Poland*

T2DM is associated with kidney disease and worsening renal function over time. SGLT2 inhibitors such as CANA act on the kidney to lower blood glucose by lowering the renal threshold for glucose, thus increasing urinary glucose excretion. This insulin-independent mechanism of action complements other therapies and may confer renoprotection. For example, EMPA-REG recently reported that an SGLT2 inhibitor slowed the rate of eGFR deterioration over 206 weeks (while eGFR declined with placebo). We used the validated ECHO-T2DM model to estimate the potential impact of SGLT2 inhibitors delaying the progression of kidney disease (as measured by the evolution of eGFR over time) on the CE of CANA vs. SU over 30 years in dual therapy with Metformin in the UK. Population characteristics, treatment effects, and adverse event rates were sourced from head-to-head data. Rescue medication consisted of insulin (basal followed by basal/bolus) when HbA1c >7.5%. Unit costs and quality-adjusted life years (QALYs) were sourced from the literature. Four scenarios were simulated: eGFR decline according to the CDC Model of CKD for both arms, eGFR constant during first 4 years of CANA treatment, eGFR constant throughout for CANA only, and eGFR constant throughout for both CANA and SU. In scenario 1, CANA 100 and 300 mg were associated with greater QALYs and greater total costs vs. SU, yielding incremental CE ratios (ICERs) of £15,280 and £12,149, respectively. ICERs declined to £11,911 and £9,368 when eGFR was held constant for 4 years and to £8,362 and £6,789 when eGFR was constant for CANA-treated patients indefinitely. Holding eGFR constant for both agents yielded similar ICERs as scenario 1. Both CANA doses were CE according to traditional metrics in the UK in all scenarios, though including the potential for SGLT2 inhibition to delay kidney disease via altering the rate of eGFR decline overtime meaningfully impacted these estimates.

Supported By: Janssen Global Services, LLC

1256-P

A Real-World Cost-Effectiveness Analysis of an Insulin Sparing Treatment Regimen

WILLIAM D. STRAIN, *Exeter, United Kingdom*

Diabetes costs approximately $320Bn per year in the U.S. Several models have suggested drugs with higher acquisition cost, but lower risk of hypoglycaemia or weight gain may be cost beneficial, but these models are limited by the cost utility estimates. *Eclipse* software monitors over 7million patient records in the UK providing a method of monitoring the cost effectiveness using real-life data.

A single practice in the UK changed its treatment strategy of T2DM in 2007 from a UKPDS based regimen (Metformin, SU and NPH insulin) to an insulin sparing regimen (Metformin, then individualized DPP-4 inhibitor, TZD or GLP-1 analogue). The *Eclipse* system monitored prescribing, unplanned admission, referral and total patient costs, compared to the local average over 7 years.

Baseline prescribing costs were low, but secondary care activity was high resulting in increased total patient cost (£4230 vs. £2100/pt/year). Instigation of the new regimen increased prescribing costs, however after five years, reductions in unplanned admissions and referral costs reduced total costs to neutrality (Table 1). Subsequent years demonstrated further reductions in costs compared to local or national average.

Using real-world data, *Eclipse* has demonstrated higher insulin sparing drug acquisition cost may be offset by reduced unplanned admissions and referral costs.

Table 1. Breakdown of the Costs per 1000 Patients in Practice Using Insulin Sparing Treatment Regimen.

Year ending	2012	2013	2014
Prescription costs*	+11.2%	+5.7%	-16.6%
Unplanned admission costs	-52%	-88%	-57.7%
Referral costs	-86.1%	-72%	N/A **
Total cost per 1000 patients	-0.7%	-5.2%	-19.7%

* Includes all prescriptions for co-morbidities in addition to diabetes related treatment costs. ** No referrals to specialists were recorded in this year. All figures are presented as percentage of local average which accounts for geographic and socio-economic factors. Where +ve figure presented that represents an increase in expenditure compared to local average, a –ve figure represents a cost saving.

1257-P

A Real-World Comparison of Outcomes in Patients Receiving Two Oral Antidiabetic Therapies, GLP-1RAs, or Basal Insulin: An Analysis of Electronic Medical Record Data

LAWRENCE BLONDE, BRICE KITIO-DSCHASSI, BRUNO GUERCI, JULIANA MEYERS, RACHELE BERRIA, MAYANK AJMERA, ELENA NIKONOVA, KEITH DAVIS, MONICA BERTOLINI, DENNIS RACCAH, *New Orleans, LA, Paris, France, Vandoeuvre Les Nancy, France, Research Triangle Park, NC, Bridgewater, NJ, Morristown, NJ, Durham, NC, Marseille, France*

Objectives: Many treatment guidelines tend to recommend and clinicians usually follow a stepwise approach that may not be ideal as patients may experience uncontrolled HbA1c between steps. Achieving HbA1c control earlier and maintaining control longer is a key goal of T2DM treatment. This study is the first in a series to assess treatment in a real world setting by comparing outcomes in patients with uncontrolled T2DM receiving 2 oral antidiabetic (OAD) therapies, GLP-1RAs, or basal insulin (BI) with a retrospective electronic medical record database.

Methods: Patients with a T2DM diagnosis between 1/1/2007 and 12/31/2014 were identified in the GE Centricity database. Patients receiving 2 OAD's, GLP-1RAs, or BI were selected (initiation of 2 OAD's, GLP-1RAs, or BI termed index date). Patients were required to have 6 months pre- and 12 months post-index date physician history and a pre-index date HbA1c >7%. HbA1c was compared between the 6 months pre- and 12 months post-index date.

Results: In total 75,366 patients met the inclusion criteria (48,965 2 OAD's, 20,457 GLP-1RAs, and 5,944 BI). The BI cohort had a higher baseline HbA1c mean [SD, median] (10.6 [2.3, 10.4)] vs. the 2 OAD's (10.1 [2.5, 9.3)] or GLP-1RAs cohorts (10.1 [2.5, 9.3)] (P<0.0001). The BI cohort had the largest decrease in HbA1c during follow-up (i.e., decrease of 3.2% for BI indicating a 30.2% change, 2.9/28.7% for 2 OAD's, and 2.7/26.7% for GLP-1RAs). Despite such marked HbA1c decrease, 58.2% of patients in the BI cohort, 51.5% in the 2 OAD's cohort and 53.5% in the GLP-1RAs cohort had HbA1c > 8.0% during follow-up.

Conclusions: In a large clinical practice database, despite improvements in HbA1c with stepwise diabetes management, over half of patients had HbA1c > 8% during follow-up, advocating the desirability of new treatment options that can provide robust and sustained glycemic control.

1258-P

Management of Inpatient Hypoglycemia: Improving Safety through The Joint Commission Standards

SHEENA CHATHA, ADELE E. CORBIN, ERIN M. SISSON, KIMBERLY M. BERGER, BRITTANY WOOLF, ANTHONY C. LEONARD, DAVID A. D'ALESSIO, MERCEDES FALCIGLIA, *Cincinnati, OH*

Numerous studies have examined the epidemiology of inpatient hypoglycemia, informing guidelines for its management. However, it is unclear how consistently hypoglycemia is appropriately managed. Timely treatment and reassessment of hypoglycemia is a target for The Joint Commission's (TJC) Certificate of Distinction in Inpatient Diabetes Care: 90% of hypoglycemic events should be re-evaluated within 30 minutes. We evaluated compliance with hypoglycemia management protocols before and after hospital-wide performance improvement (PI) strategies.

Using a daily report of hypoglycemic (BG < 70 mg/dl) events at a 600-bed academic hospital, we determined the time to reassessment after hypoglycemia. Over 3 16-week blocks, December 2014 to December 2015, PI interventions targeting all levels of the organization were implemented including; review of data at management and executive leadership meetings, daily hypoglycemia reassessment reports to individual units for real-time feedback and accountability, computer and classroom education, reminder badges, tokens of recognition that were educational, and a template for documentation.

There were 2984 hypoglycemia episodes, of which 26% were ≤ 50 mg/dl. Rates of reassessment improved from blocks 1 to 3: 67, 71, 74% (p = 0.0004). Reassessment rates within 60 minutes also improved: 83, 86, 89% (p=0.0002). For hypoglycemia ≤50 mg/dl, there was a trend toward improvement in the 30-minute reassessment and TJC goals were met in block 3: 86, 87, 91% (p=0.06).

Implementation of hospital-wide interventions was associated with significant improvements in hypoglycemia reassessment. These outcomes all approached TJC goals. Furthermore, increased 60-minute reassessments demonstrate an improvement in timeliness. These findings suggest that staff are more likely to appropriately manage hypoglycemia if severe. Asymptomatic, milder hypoglycemia may elicit less concern from staff, indicating an area for additional education.

1259-P

Assessment of a Long-Term Outcome of a Residential Camp on Diabetes Management in Rwanda

LAURIEN SIBOMANA, TREVOR J. ORCHARD, *Pittsburgh, PA*

In the past 5 yrs, type 1 diabetes care in Rwanda has been improving; the number of patients receiving care has increased from < 300 to > 1000. This improvement is due to a collaboration between Rwanda Diabetes Association (RDA), the IDF's Life for A Child (LFAC) program, the University of Pittsburgh, Marjorie's Fund (MF), Team type 1, and importantly the Government of Rwanda (GoR). With patients now living longer and due to the IDF/LFAC's program age limit of 25 yrs it is expected that by the end of 2016 more than 400 young adults with diabetes will be without IDF/LFAC support, putting them at increased risk of diabetes complications. To alleviate this issue the RDA runs a residential Diabetes Educational Center (DEC) with MF's assistance. Up to 20 young adults spend 6 months on vocational training and learn how to better manage and cope with diabetes. To assess the long- term outcome of the DEC on diabetes management, HbA1c for 53 former center attendees: 2013 (16), 2014 (19) and 2015 (18) was recorded in each individual's RDA file. HbA1c were measured at center enrollment, at discharge, and up to 2 yrs after discharge. Average A1c at enrollment and at discharge was reduced from 10.94 to 8.76 (p=0.014); 9.86 to 7.00 (p=0.002); and 10.20 to 7.10 (p=0.000) respectively. However as time after center increases, the observed HbA1c reduction is attenuated (latest average A1c 9.55; 8.75; and 7.81 respectively). At the center, attendees check their blood sugars up to 6x a day, while at home they usually do so only ≤2x, citing unavailability, inaccessibility or unaffordability of insulin, monitoring items and/or food. Based on these results, when insulin, blood sugar testing materials, and food are available, optimum diabetes management can be achieved in limited resources settings and residential diabetes center proves to be an effective venue to learn diabetes management. However, more regular follow up after graduating from the center is needed to help maintain the improvements made.

1260-P

WITHDRAWN

For author disclosure information, see page A696.

1261-P

Health Care Resource Utilization between Physician and Non-Physician Primary Care Providers for Outpatient Diabetes Care Delivery

SALIM S. VIRANI, JULIA M. AKEROYD, DAVID J. RAMSEY, KHURRAM NASIR, SUJA RAJAN, ANITA DESWAL, CHRISTIE M. BALLANTYNE, LAURA A. PETERSEN, *Houston, TX, Miami, FL*

Although effectiveness of diabetes care (attainment of performance measures) between physicians and non-physicians (nurse practitioners, physician assistants) has been shown to be comparable, resource utilization for diabetes care between these two provider types is not known.

We identified diabetes patients with outpatient primary care visits between October 2013 and September 2014 in 130 Veterans Affairs facilities. Using hierarchical regression adjusting for patient illness-burden and other covariates, we compared number of primary or specialty care visits, and number of lipid panels and HbA1c tests performed among patients receiving care from physicians (n=811,872) and non-physicians (n=210,716).

Physicians had significantly larger panel size (mean=1039.5) compared with non-physicians (mean=872.3, p<0.0001). In adjusted analyses (Table), patients receiving care from non-physicians received more frequent lipid and HbA1c testing and less frequent primary or specialty care visits. Most of these differences although statistically significant were numerically small and clinically insignificant.

Health care resource utilization for diabetes care delivery among non-physicians is at least comparable (and lower for some measures) compared with physicians, although, physicians work with much larger patient panels.

Table.

Health care resource utilization measure	Patients receiving care from physician providers (n= 811,872)	Patients receiving care from non-physician providers (n=210,716)	Beta coefficient * (95% CI) (adjusted) ** [patients receiving care from physicians as referent]
Number of primary care visits per patient in the past year (mean/SD)	5.12/5.19	4.94/4.99	-0.014 (-0.016 to -0.012)
Number of specialty care visits per patient in the past year (mean/SD)	0.21/0.98	0.20/0.93	-0.013 (-0.024 to -0.001)
Number of lipid panels in the past year or within 2 weeks per patient following last primary care visit (mean/SD)	1.72/1.06	1.74/1.05	0.039 (0.035 to 0.042)
Number of HbA1c tests in the past year or within 2 weeks per patient following last primary care visit (mean/SD)	2.00/1.17	2.05/1.18	0.037 (0.033 to 0.040)

*Beta coefficients can be interpreted as the unit increase in the dependent (outcome variable) associated with a non-physician provider (compared with physician provider). For e.g., patients with diabetes receiving care from non-physicians in this sample have on average 0.014 fewer primary care visits compared with those receiving care from physicians after adjustment for other covariates in the model. **Adjusted for age, gender, race (whites vs. others), history of hypertension, diagnostic cost group relative risk score (a marker of patient's overall illness-burden), teaching vs. non-teaching facility, and history of CVD (IHD, ICVD or PAD), plus clustering at the facility level. CI = confidence interval, SD= standard deviation, CVD = cardiovascular disease, ICVD = ischemic cardiovascular disease, PAD = peripheral artery disease.

Supported By: American Diabetes Association (1-14-CE-44 to S.S.V.); U.S. Department of Veterans Affairs

1262-P

Do Financial Incentives Make a Difference in Outcomes for Medicaid Members in the DPP?

SARAH M. BROKAW, DOROTA CARPENEDO, PAUL CAMPBELL, STEVEN D. HELGERSON, TODD S. HARWELL, MONTANA DIABETES PREVENTION PROGRAM WORKGROUP, *Helena, MT*

Few studies have evaluated the impact of financial incentives (INC) to promote participation in weight loss programs and weight loss outcomes among high-risk low-income populations. Between 2012-2015 the MT Diabetes Prevention Program (DPP) enrolled 261 adult Medicaid members at high-risk for CVD and/or type 2 diabetes into our group-based intensive lifestyle intervention. We utilized a crossover design to investigate whether providing small incremental financial INC (up to $320 maximum per participant) increased attendance, behavior changes, and achievement of the 7% weight loss goal compared to members not receiving INC. Demographic characteristics were similar between the two groups (Table). Participants in the INC group attended more visits, had greater completion rates, reported greater physical activity levels, and self-monitored fat more frequently than the non-INC group. At the end of the core session, participants in both groups had achieved significant weight loss (Table); however, there were no significant differences in weight loss between the groups. Our findings suggest that it is feasible to enroll adult Medicaid members into an adapted DPP and that these participants can achieve significant weight loss. Members receiving financial INC had higher participation rates and weight loss associated behavior changes, but did not achieve significantly greater weight loss than the non-INC group.

Table. Participant Characteristics and Outcomes During the 16-week Core, by Intervention Group, Montana DPP, 2012-2015.

	Non-INC Group (N = 107)	INC Group (N = 154)
	Mean (SD)	Mean (SD)
Age (Years)	45.2 (12.8)	45.5 (12.5)
Baseline BMI (kg/m^2)	40.8 (10.1)	39.7 (8.8)
Sessions attended	12.3 (6.6)	14.5 (6.7) **
Physical activity (minutes/week)	163.1 (85.7)	180.5 (101.7)
BMI change (kg/m^2)	-0.8 (1.8)	-1.3 (1.6)
Weight change (kg)	-2.2 (3.9)	-2.2 (5.1)
	% (n)	% (n)
Sex (Female)	77 (82)	78 (120)
Disability (one or more)	62 (58)	53 (81)
Completed DPP	47 (50)	60 (92) *
Met physical activity goal	51 (42)	65 (88) *
Self-monitored fat intake 14-16 weeks	6 (4)	19 (25) **
Achieved 5% WL	17 (18)	24 (36)
Achieved 7% WL goal	12 (13)	12 (18)

*p<0.05; **p<0.01.

Supported By: Centers for Medicare & Medicaid Services

1263-P

The 2015 IDF Diabetes Atlas Estimates of the Cost of Illness in North America

JOAO DIOGO DA ROCHA FERNANDES, KATHERINE OGURTSOVA, DAVID CAVAN, LYDIA E. MAKAROFF, IDF ATLAS GROUP, *Brussels, Belgium*

Diabetes imposes enormous human and economic costs. In 2015, 44 million adults were living with diabetes in the IDF North American and Caribbean Region (NAC). The NAC Region consists of the U.S., Mexico and Canada, and 25 Caribbean countries and territories.

As the WHO predicts that globally diabetes will be the 7th leading cause of death by 2030, it is essential to estimate the annual health-care expenditures due to this disease, in order to correctly plan and allocate resources.

The IDF Diabetes Atlas 2015 diabetes-related health expenditures on diabetes were estimated by using UN population estimates (2015), UN Mortality rates (2006), IDF Diabetes Atlas prevalence estimates (2015), WHO total health expenditure estimates (2013), and diabetes cost-ratios (KPNW diabetes registry, 2004). The analysis was based on a logistic regression model, which adjusted for the cost of care for different age groups, and gender.

It was estimated that USD348 billion were spent on diabetes-related healthcare expenditure in the NAC region in 2015. After adjusting for purchasing power, this accounted for 44% of global diabetes-related health spending. If per-capita spending remains consistent, the total diabetes-related health expenditure in the region will reach USD390 billion by 2040.

There were great disparities in health spending between countries. Within the NAC region, the country with the lowest health expenditure per person with diabetes was Haiti, with 275 International Dollars (ID) spent in 2015. The country with the highest health expenditure per person with diabetes was the U.S., with ID 10,942 spent. In the NAC region, diabetes-related healthcare expenditure accounted for 14% of the total healthcare budget, while the world average was 12%.

Diabetes-related health expenditures accounted for 1 dollar in 7 of the total healthcare budget within the NAC region. These funds must be utilized more efficiently to prevent type 2 diabetes, and treat diabetes in a cost-efficient manner.

Supported By: AstraZeneca; Lilly Diabetes; Merck & Co., Inc.; Novo Nordisk Inc.

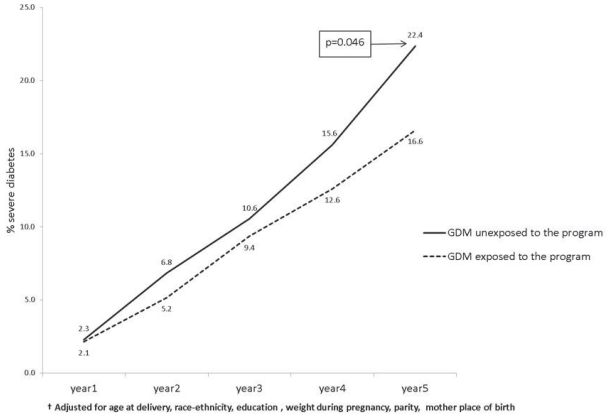
1264-P

Effectiveness of a Health System Program in Delaying the Onset of Severe Diabetes among Women with Gestational Diabetes (GDM)

ASSIAMIRA FERRARA, JULIE A. SCHMITTDIEL, SUSAN D. BROWN, MONIQUE M. HEDDERSON, JUANRAN FENG, ALYCE ADAMS, JENNY CHING, YVONNE CRITES, ROMAIN NEUGEBAUER, *Oakland, CA*

We evaluated a program for screening, prevention and early treatment of diabetes among postpartum women with history of GDM. Within an integrated health care delivery system a postpartum program including the use of an OGTT for screening along with a step-wise approach for prevention of diabetes (mailed lifestyle recommendations and referral to prediabetes classes) and early treatment of diabetes was implemented in 2006. We compared the adjusted cumulative incidence of screen detected diabetes and severe diabetes (defined by A1c>8%) between women with a GDM pregnancy in 2006-2010 (n= 5,888) who were unexposed to the program and women with a GDM pregnancy in 2001-2005 (n= 4,690) exposed to the program by using inverse probability weighting methods. The adjusted cumulative incidence of diabetes did not differ between exposed and unexposed (36.1% vs. 36.9%). However, women exposed had lower 5-years adjusted cumulative incidence of severe diabetes than women unexposed to the program (16.6% vs. 22.4%, p= 0.046; Figure). The greater sensitivity of screening by OGTT likely led to a greater identification of diabetes. However, exposure to the program including the use of OGTT for early detection of diabetes and prediabetes along with the prevention follow-up of women with prediabetes, and the early treatment of diabetes was associated with a reduction of severe diabetes.

Figure. Adjusted Cumulative Incidence of Severe Diabetes by Year Postpartum.



Supported By: Centers for Disease Control and Prevention; National Institute of Diabetes and Digestive and Kidney Diseases

1265-P

Diabetes and QVIs: Measuring Variation in the Quality of Hospital Care

JANIS E. BOZZO, JOAN M. RIMAR, CATHERINE M. VISCOLI, STEPHEN ALLEGRETTO, KARRIE C. HENDRICKSON, THOMAS J. BALCEZAK, SILVIO E. INZUCCHI, *New Haven, CT*

Hospitalized patients (pts) with diabetes (DM) are at increased risk of adverse clinical outcomes. An emerging metric to assess the quality of inpatient care, Quality Variation Indicators (QVI®s) was developed to quantify/compare potentially avoidable inpatient complications. QVIs comprise a taxonomy based on ICD codes for adverse events. Their presence reflects variances in care quality and correlates with increased costs and length of stay (LOS). Heretofore, there have been no data reported on QVIs in hospitalized pts with DM. We analyzed QVIs at our 1,571-bed academic hospital over a single fiscal year (FY) in pts with and without DM.

Among 63,751 FY2014 adult discharges, 15,340 (24.1%) had DM; 1,392 had QVIs (9.1%) compared to 7.1% of adult discharges without DM (Relative Risk [RR] 1.28, 95% CI, 1.21, 1.36; p<0.0001). Data were similar after omitting the QVI category pertaining to DM complications (1,384 (9.0%) discharges, RR 1.27 [1.20, 1.35; p<0.0001)]. Adjusting for admitting department only modestly decreased the association (Mantel-Haenszel RR 1.21 [1.14, 1.29; p<.0001)]. Of pts with QVIs, there was a trend for those with DM to register in multiple QVI categories (28.8% vs. 24.2%, p=0.08). The largest departments (>500 discharges/year) with the greatest QVI difference between DM and non-DM pts included Cardiac Surgery (25.2% vs. 17.0%), Pulmonary/Critical Care (40.4% vs. 34.9%), and Otolaryngology (15.8% vs. 8.3%). DM pts with QVIs had a 3.8-fold increase in hospital direct costs as compared to DM pts without QVIs ($31,381 vs. $8,192) and a 9.7 day increase in average LOS (14.8 vs. 5.1). The corresponding numbers in non-DM pts were 3.7 ($27,510 vs. $7,398) and 9.0 days (13.5 vs. 4.5). The 305 excess discharges in DM pts with QVI®s resulted in >$7 million in excess direct costs.

Hospitalized pts with DM have a greater QVI frequency, which appears linked to higher costs and longer LOS. These data will allow us to determine the nature and origin of these variances and to develop appropriate interventions.

1266-P

Correlation between Provider Use Rates of a Clinical Decision Support Tool and Diabetes Performance Measures

DARIN RUANPENG, JOANN M. SPERL-HILLEN, PATRICK J. O'CONNOR, STEPHEN E. ASCHE, HEIDI L. EKSTROM, *Saint Paul, MN, Minneapolis, MN*

A previously published randomized controlled trial demonstrated that implementation of an electronic health record-linked personalized clinical decision support (PCDS) tool within primary care clinics improved mean A1c and BP control. We subsequently implemented a modification of the CDS for expanded use with high cardiovascular risk adults (CV-PCDS) that also retained the decision support for glycemic control for patients with diabetes. Here we analyze the association between primary care provider use rates of CV-PCDS with diabetes performance measures in patients with diabetes. Using data from a cluster randomized trial in 2012-2014, we analyzed the association of CV-PCDS provider-specific use rates in March 2014 with diabetes performance measures 6 months later, using Pearson correlation coefficients. Performance measures included the proportion of a provider's diabetes patients who (a) achieved A1c < 8%, and (b) achieved a composite measure of optimal diabetes care (ODC) that required simultaneous achievement of A1c < 8%, SBP < 140 mm Hg, LDL < 100 mg/dl, non-tobacco user, and ASA use for secondary prevention. Providers (N=43) used the CV-PCDS tool at a mean of 82.1% of targeted encounters of adults with high CV risk (range across providers 36.0% to 100% of encounters). The mean percentage of the diabetes subgroup who achieved A1c <8% was 73.7%, and the percentage of patients who achieved the ODC goal was 46.8%. Pearson correlation coefficients between March 2014 CV-PCDS provider use rates and A1c and ODC performance measures in August 2014 were 0.16 (p=0.31) and 0.24 (p=0.12) respectively. In this high-performing health care system with high CV-PCDS use rates, there was a positive but non-significant association of provider use of the CV-PCDS tool and provider-level quality of diabetes care 6 months later. The generalizability of this finding to lower-performing care systems, and to providers with lower baseline quality of diabetes care remains to be determined.

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1267-P

Improving Performance of Primary Care Teams Treating and Managing Diabetes

SUZANNE MURRAY, IVAN DESVIAT, PATRICE LAZURE, LUIS ALBERTO VAZQUEZ, MARTA LÓPEZ CANO, CARLOS PESQUERA, *Brossard, QC, Canada, Madrid, Spain, Santander, Spain*

The European Performance Improvement in Diabetes Demonstration project (EPIDD) was an initiative deployed in the region of Santander, Spain, to demonstrate the impact of a local Performance Improvement (PI) program to improve clinical practice of Primary Care teams providing care to type 2 diabetes (T2D) patients. In Phase 1, potential practice challenges were identified from a literature review. In Phase 2, a consultation group of local healthcare providers and decision-makers prioritized the locally relevant challenges, which were validated during semi-structured interviews with Nurses and Physicians (n: 25). Four challenges were retained (see Table

For author disclosure information, see page A696.

1) for the live case-based educational interventions designed and deployed in three clinics (n: 43) during Phase 3. Cases were designed based on difficult clinical scenarios provided by the learners themselves during Phase 2 interviews. The ethics-approved evaluation (phase 4) included a 10-minute online survey with learners (n: 25), and 45-minutes qualitative interviews with learners, clinic administrators and T2D patients (n: 33). Increased knowledge and skill were reported, as well as changes in practice (see Table 1). The success of this demonstration project suggests that the four-phase PI approach could be replicated in other clinical settings and/or at a larger scale.

Table 1. Challenges Targeted by the Intervention and Evaluation Findings.

Challenges Retained for the Intervention	Results Reported
I. Diagnostic uncertainties and challenges related to patient uptake of diagnosis	- Low levels of knowledge gained - No change in clinical practice - Reported enhanced Patient-Provider communication (should help providers ensuring uptake of diagnosis)
II. Challenges related to insulin therapy and therapeutic inertia	- Decrease of therapeutic inertia - Increase of confidence using different types of insuins/mixtures - Increase knowledge of communication strategies to alleviate patient fears - Enhanced skills and confidence in Patient-Provider Communication to discuss insulinization with patients - More complex cases kept in primary care, reducing referrals to specialists
III. Empowering patients to make lifestyle changes	- Increase of confidence discussing lifestyle changes with patients - Enhanced Patient-Provider communication should help providers better support patients
IV. Challenges in pro-active management of T2D complications (Diabetic foot and hypoglycemia)	- Improved awareness of importance of annual check-up for diabetic foot - Increase of knowledge, confidence and skills in management of hypoglycemia and diabetic foot - Patient group on diabetic foot was put in place in one of the clinics

Supported By: Eli Lilly and Company

1268-P

Hyperglycemic Emergencies in Young Adults with Diabetes in an Inner-City County Hospital

J. SONYA HAW, MARY K. FINDLEY, EUN SEOK CHA, MELISSA FAULKNER, FARAH KHAN, SARA C. MARKLEY, ANASTASIA-STEFANIA ALEXOPOULOS, SUDESHNA PAUL, MOHAMMED K. ALI, *Atlanta, GA*

Nationally, diabetes (DM) control is poorer among young adults; however, little is known about the relative impact of control on hospital admissions and complications. We used retrospective electronic medical record data from Grady Memorial Hospital (GMH), a large inner-city county hospital in Atlanta, GA to describe characteristics of a random sample of young adults (YA) aged 18-35 years who were admitted for hyperglycemic emergencies from 2010-2014. We used linear and logistic regression to explore if and how admission A1c and blood glucose (BG), insurance status, and mental health (MH) comorbidity were associated with hospital complications and ICU stay.

From 2010-2014, there were 2,458 total admissions for either Diabetic Ketoacidosis (DKA) or Hyperglycemic Hyperosmolar Syndrome (HHS). Of these, 29% were among 18-35 year olds. Of 1,045 readmissions for either DKA or HHS, the proportion among YAs was 54% vs. 38% in adults >35 years. Among 155 randomly selected first admissions in YAs, mean age was 24.8±4.4 years (age at DM diagnosis 17.8±8.2 years), 50% were male, 84.5% black, BMI 26.8±7.9kg/m^2, and A1c at admission was 12.7±2.5%. 76% had type 1 diabetes and 60.8% had documented MH conditions. 44.1% were insured, but 71% had no clinic visit within 12 months prior to admission. Having insurance was associated with lower admission A1c (B = -1.6, p = .006). There was no significant association between admission A1c and hospital complications or LOS, though higher admission BG was associated with more hospital complications (B = .002, p=.009). Those with MH conditions had 56% more hospital complications (p=.014) and longer ICU stay (B = .39, p=.027).

High proportions of DKA/HHS admissions and readmissions occur in YAs; and MH comorbidities are associated with higher hospital complications and prolonged ICU stays. Further research on interventions are key for addressing MH conditions that may influence DKA/HHS-related complications in the YA population who lack insurance and regular clinic visits.

1269-P

Wishes for Improvement in Social Conditions Regarding Diabetes among U.S. Ethnic Groups

ROBERT A. GABBAY, LEONARD EGEDE, MARTHA FUNNELL, WILLIAM C. HSU, MARK PEYROT, *Boston, MA, Charleston, SC, Ann Arbor, MI, Baltimore, MD*

Aims: To determine ethnic group perceived need for major improvements in social conditions regarding diabetes (DM).

Methods: The 2nd Diabetes Attitudes, Wishes and Needs (DAWN2) Study assessed perceived need for improvement in social conditions regarding DM among 1055 adult people with diabetes (PWD) and 238 adult family members (FM) from 4 ethnic groups: White non-Hispanics (PWD/FM = 447/105), African Americans (241/47), Hispanic Americans (194/46), Chinese Americans (173/40).

Results: Overall, PWD and FM ranked 5 areas assessed in the same order from highest to lowest need: Places to buy health/affordable food (PWD/FM = 56%/57%), Earlier DM diagnosis/treatment (53%/53%), Convenient/safe places to exercise (43%/44%), Workplaces that facilitate DM self-management (35%/32%), Acceptance of PWD in society (30%/22%). For PWD (16%-45% vs. 39%-69%) and FM (10%-41% vs. 22%-80%), white non-Hispanics rated the need for improvement lower than all ethnic minority groups for all indicators. Among PWD, ethnic minority groups reported levels of need for improvement that were similar to each other for each indicator. Among FM, Chinese Americans reported more need for improvement than African Americans and Hispanic Americans for all indicators. FM were asked about 3 additional needs for improvement, each of which was endorsed by over half of respondents: Good medical care for DM (61%), Prevention of DM (59%), Public awareness of DM (52%). White non-Hispanic FM identified less need (36%-46%) and Chinese American FM identified more need (78%-83%) than other ethnic groups for each of these indicators.

Conclusions: White non-Hispanic PWD and FM in the U.S. identified less need than ethnic minority groups for all social indicators. It appears that efforts to improve social conditions regarding diabetes should prioritize ethnic minority communities and populations.

Supported By: Novo Nordisk Inc.

1270-P

Quality of Care of the Initial Patient Cohort of the Diabetes Collaborative Registry

SUZANNE V. ARNOLD, SILVIO E. INZUCCHI, DARREN K. MCGUIRE, SANJEEV N. MEHTA, ABHINAV GOYAL, LAURENCE S. SPERLING, THOMAS M. MADDOX, DANIEL EINHORN, NATHAN D. WONG, PETER FENICI, NIKLAS HAMMAR, JOHN J. SHEEHAN, JENNIFER L. WONG, MIKHAIL N. KOSIBOROD, *Kansas City, MO, New Haven, CT, Dallas, TX, Boston, MA, Atlanta, GA, Denver, CO, San Diego, CA, Irvine, CA, Rome, Italy, Mölndal, Sweden, Fort Washington, PA, Washington, DC*

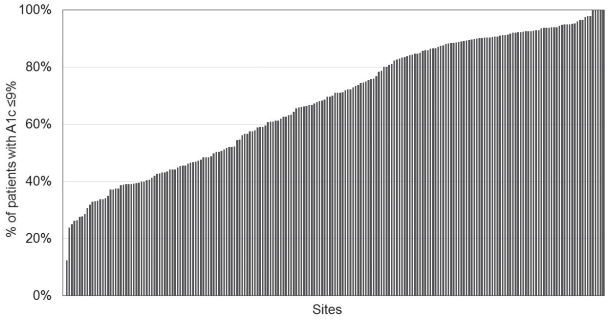
Background: Although guidelines and performance measures exist for patients with DM, adherence to these metrics is not well known. The Diabetes Collaborative Registry® (DCR) was formed to understand the quality of DM care across the primary and specialty care continuum.

Methods: DCR is comprised of primary care, endocrinology, and multispecialty practices. Due to an established IT integration, cardiology sites predominate the initial data sample (>90% of sites). We assessed the average rate of adherence to 7 DM quality metrics and variability across the DCR sites. The last visit in the prior year was used for analysis.

Results: Average adherence to DM quality metrics across 236 practices with 861,699 patients: 1.) A1c checked and ≤9%: 20%; 2.) ACE-I or ARB: 73%; 3.) screening for nephropathy: 70%; 4.) BP <140/90 or on ≥2 antihypertensives: 89%; 5.) screening for smoking and counseling smokers to quit: 85%; 6.) eye exam: 11%; 7.) foot exam: 1.2%. Among patients with A1c data, the average rate of A1c ≤9% across sites was 67.8% (range 0-100%, Figure).

Conclusions: The DCR was formed to document and improve the outpatient management of DM. While performance on some metrics (BP control) was high, adherence to others (glycemic control) remains suboptimal and highly variable. This may be attributable to predominance of cardiology sites (e.g., ownership of eye/foot exam), lack of documentation, true gaps in care, or a combination of these factors.

Figure. Variability in Glycemic Control Across Practices in DCR.



1271-P

Does Inpatient Management of Stress Hyperglycemia and Diabetes Mellitus Influence In-Hospital Outcomes and Survival?

ALESSANDRA DEI CAS, VALENTINA RIDOLFI, RAFFAELLA ALDIGERI, ANNA VITTORIA CIARDULLO, VALERIA MANICARDI, ALESSANDRA SFORZA, FRANCO TOMASI, DONATELLA ZAVARONI, RICCARDO C. BONADONNA, IVANA ZAVARONI, *Parma, Italy, Modena, Italy, Reggio Emilia, Italy, Bologna, Italy, Ferrara, Italy, Piacenza, Italy*

In-hospital management of stress hyperglycemia and diabetes is complex and requires specific expertise of physicians and nurses.

The aim of this study was to assess the management of inpatients with stress hyperglycemia or diabetes and to investigate its relationship, if any, with clinical outcomes.

A total of 814 patients from 3 different types of wards - Internal Medicine (IM, n=2, patient n=304), General Surgery (SU, n=2, patient n=267) and Intensive Care (IC, n=2, patient n=243) Units - of 6 hospitals of Emilia Romagna region (Italy) were enrolled.

A work-flow of clinical care of stress hyperglycemia/diabetes was created according to national and international guidelines. The workflow was divided in 5 different domains: 1.) initial assessment, 2.) glucose monitoring, 3.) medical therapy, 4.) consultancies, 5.) discharge. Each domain was assessed by a performance score (PS), computed as the sum of the scores achieved in a set of indicators of clinical appropriateness, management and, only in domain 5, end points. Clinical outcomes included: hypoglycemia, achievement of glycemic goals, survival rate and conditions at discharge. The PS of initial assessment and glucose monitoring were significantly lower in SU respect to IM and IC ($p<0.0001$). The PS of initial assessment and glucose monitoring were also associated with achievement of glycemic goals (OR 1.53 $p<0.0001$) and lower risk of hypoglycemia (OR 0.62 $p<0.0001$), respectively, in a model adjusted for age, gender, admission glycemia, ward type and Charlson comorbidity index. Furthermore, the PS of initial assessment and diabetologic consultancy were associated with increased survival rate (OR 1.59, $p=0.009$; OR 4.02, $p=0.02$). The PS of initial assessment was also related to better discharge conditions (OR 1.63, $p=0.002$).

We conclude that the quality of in-hospital care of stress hyperglycemia/diabetes may affect patient outcomes, including survival.

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PEDIATRICS—OBESITY AND TYPE 2 DIABETES

Moderated Poster Discussion: Novel Concepts in Pediatric Obesity and Type 2 Diabetes *(Posters: 1272-P to 1278-P), see page 21.*

1272-P

Clinical Characteristics in Children with Renal Glucosuria Detected by Urine Glucose Screening Program at School in Tokyo

TATSUHIKO URAKAMI, YUSUKE MINE, MASAKO AOKI, MISAKO OKUNO, JUNICHI SUZUKI, *Tokyo, Japan*

Renal glucosuriais (RG) is known to be a rare condition with decreased renal tubular resorption of glucose in the absence of hyperglycemia. In some affected families, RG results from gene mutation of SGLT2 in renal tubule. On the other hand, we have annual urine glucose screening program at school, and have detected children with diabetes at the early stage. We also have identified some cases with RG based on a positive result for glucosuria with normal glucose metabolism. We hereby report clinical characteristics in children diagnosed with RG by the screening program in Tokyo from 2010 to 2015. During the study period, 986,614 children, 6-15 years old, participated in the screening program, and 150 showed positive results for glucosuria. We performed OGTT in combination with measurement of HbA1c to confirm diabetes. As a result, 37 children were diagnosed as diabetes, and 111 were finally identifies as RG without the evidence of hyperglycemia. Prevalence of RG was estimated as 11.2/100,000 in schoolchildren. Frequency of male was 51%, and the mean age at diagnosis was 11.1±2.6 years. Thirteen (11.7%) children had overweight (more than 120% of ideal weight), whereas only one (0.9%) had underweight (less than 80% of ideal weight). Two third had family members suspecting to have RG in the first- and second-degree relatives. All cases showed normal glucose tolerance (FPG 94.8±6.6 mg/dL, HbA1c 5.4±0.2%) in the absence of insulin resistance (HOMA-R 1.6±1.4) and impaired insulin secretion (HOMA-β 79.0±62.5). In conclusion, RG is revealed not a rare condition among schoolchildren with glucosuria. The disorder seems to be strongly inherited and to show less commonly body weight loss despite continually excretion of glucose in urine.

1273-P

Therapeutic Inertia: Underdiagnosed and Untreated Hypertension and Dyslipidemia in the Pediatric Diabetes Consortium (PDC) Type 2 Diabetes (T2D) Registry

MICHELLE VAN NAME, WILLIAM V. TAMBORLANE, PEIYAO CHENG, ROBIN L. GAL, CRAIG KOLLMAN, ROY W. BECK, COURTNEY ENGLE, LIANA HSU, JANET SILVERSTEIN, STEVEN M. WILLI, PEDIATRIC DIABETES CONSORTIUM, *New Haven, CT, Tampa, FL, Los Angeles, CA, Stanford, CA, Gainesville, FL, Philadelphia, PA*

Despite the high prevalence of hypertension and dyslipidemia in youth with T2D observed by the TODAY study, the frequency of these comorbidities and the effectiveness of their management in a clinical care setting have not been established. Medical records of 650 patients with youth onset type 2 diabetes at the time of enrollment into the PDC T2D Registry, were analyzed using a logistic regression model. Hypertension was defined by a diagnosis in the medical record, drug treatment for hypertension, or systolic or diastolic blood pressure (BP) ≥95th percentile for age <18 years (or systolic ≥140 or diastolic BP ≥ 90 for those age 18 and above). Dyslipidemia was defined as a diagnosis in the medical record, drug treatment for dyslipidemia, or non-HDL cholesterol ≥ 145 mg/dL. The prevalence of hypertension and dyslipidemia were 30 and 44%, respectively. Hypertension prevalence was associated with increased BMI ($p<0.001$), while prevalence of dyslipidemia was associated with increased age ($p=0.02$) and HbA1c ($p<0.001$). The prevalence of hypertension and dyslipidemia were not affected by T2D duration. Of note, only 47% of hypertension patients and only 44% of dyslipidemia patients carried these diagnoses in the medical record. Moreover, only 32% of the hypertension participants and 10% of dyslipidemia participants had evidence of drug treatment. Hypertension and dyslipidemia are common comorbidities in youth with T2D. Despite a high prevalence, fewer than half of affected patients were identified as having these conditions and less than one third were receiving drug therapy.

Supported By: Novo Nordisk Inc./Boehringer Ingelheim

1274-P

Sleep Duration and Cardiometabolic Risk in Children and Adolescents: Does Adipokines Play a Mediating Role?

MING LI, LUJIAO LI, SHAN GAO, JUNLIN FU, WENHUI LI, BCAMS, *Beijing, China*

The aim was assess the association of sleep duration with adipokine levels and cardio-metabolic risk factors and the possible mediating roles of adipokines, in a cohort of Chinese school-aged children. Sleep duration was collected through questionnaires in Beijing Child and Adolescent Metabolic Syndrome cohort study. A total of 3206 children were analyzed in two age groups: 6-12 years old and 13-18 years old. Adipokines were determined by ELISA, including leptin, total and high molecular weight (HMW) adiponectin, resistin, Fibroblast Growth Factor-21 (FGF-21), retinol binding protein 4 (RBP4), and secreted protein acidic and rich in cysteine. Among the 6-12 years old children, after adjusted for covariates, short sleep duration was associated with higher ln leptin (β= - 0.188; $P < 0.001$), ln FGF-21 (β= - 0.082; $P = 0.041$), and lower ln HMW-adiponectin (β= 0.045; $P = 0.006$); the association with leptin remained significant even further adjusted for BMI ($P < 0.05$). Meanwhile, short sleep duration was associated with increased BMI (β= -0.607; $P < 0.001$), waist circumference ($P < 0.001$), fasting glucose (β= -0.058; $P < 0.001$), in HOMA-IR (β= -0.094; $P < 0.001$), in triglyceride ($P = 0.023$), and lower HDL-C ($P = 0.008$); moreover, the significance of these associations, except for fasting glucose ($P < 0.001$), was disappeared (all $P > 0.05$) after further adjusted for leptin. For the 13-18 years old group, short sleep duration was associated with high ln RBP4 (β= -0.017; $P = 0.032$), BMI ($P = 0.014$), waist circumference ($P = 0.007$) and fat percentage (P =

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

0.011), but the significance of association with RBP4 was remarkably attenuated after further adjusted for BMI (P=0.067). In conclusion, short sleep duration has a substantial relationship with obesity along with adverse adipokine secretion pattern among Chinese children. The associations between sleep duration and cardio-metabolic risk appear to be more remarkable exclusively in younger children, and could be at least partly explained by leptin.

Supported By: Beijing Municipal Science & Technology Commission; Novo Nordisk Inc.; National Key Program of Clinical Science (to M.L.)

1275-P

Malaysian Youth with Type 2 Diabetes, Characterized by Reduced Insulin Sensitivity and Secretion, Have also Impaired Incretin Effect

TOH PENG YEOW, GIOVANNI PACINI, ANDREA TURA, CHEE PENG HOR, JANET YEOW HUA HONG, SHUEH LIN LIM, FLORENCE HUI SIENG TAN, CHIN VOON TONG, FUZIAH M.D. ZAIN, JENS JUUL HOLST, WAN NAZAIMOON WAN MOHAMUD, *Penang, Malaysia, Padova, Italy, Putrajaya, Malaysia, Sarawak, Malaysia, Copenhagen, Denmark, Kuala Lumpur, Malaysia*

Type 2 diabetes (T2DM) among the youth is a rising phenomenon. The pathophysiology has been studied primarily on non-Asian populations while literature on incretin effect is scarce. We evaluated insulin sensitivity, beta-cell function, incretin hormones and their effect in youth with T2DM from a multiethnic Malaysian population.

25 youth with T2DM (fasting glucose 9.9±0.85 mmol/l) and 15 controls (glucose 4.5±0.06, p<0.001) underwent a 2-hour oral glucose tolerance test (OGTT) and a 1-hour intravenous glucose tolerance test (IVGTT). Insulin sensitivity was derived from QUICKI, oral glucose index (OGIS) in OGTT and the surrogate index of SI from the minimal model (CSI) in IVGTT. Acute insulin response (AIR) was obtained from IVGTT. Total beta-cell function (BC) was computed as $\Delta AUC_{insulin}/\Delta AUC_{glucose}$, during OGTT ($BC_{OG}$) and IVGTT ($BC_{IV}$), respectively; disposition index as CSI x AIR. GLP-1 response was calculated as ΔAUC_{GLP-1}. Dimensionless incretin effect was estimated as BC_{OG}/BC_{IV}.

Results are shown in the Table. The T2DM group had lower insulin sensitivity and beta-cell function. Despite identical GLP-1 response, the incretin effect was reduced in the T2DM group. T2DM has lack of compensatory mechanisms, as shown by the disposition index. This may be partly ascribed to the impaired incretin effect, observed without reduction in GLP-1, similar to that of adult T2DM.

Table.

	T2DM (n=25)	Control (n=15)	*p*-value
Age (years) (M:F)	18.5±0.92 (12:13)	22.0±0.85 (7:8)	0.008
Malay:Chinese:Others	16:6:3	12:2:1	
BMI (kg/m^2)	30.2±1.05	27.3±1.08	0.081
HbA_{1c} (%)	8.4±0.37	5.3±0.09	<0.001
Waist-hip ratio	0.9±0.01	0.8±0.02	0.011
Triglycerides (mmol/L)	1.6±0.14	1.1±0.17	0.040
LDL-C (mmol/L)	3.7±0.21	3.3±0.20	0.289
HDL-C (mmol/L)	1.2±0.06	1.5±0.08	0.012
hsCRP (mg/L)	3.8±0.73	1.6±0.41	0.01
Albuminuria	14 (56.0)	0	<0.001
QUICKI	0.21±0.01	0.27±0.01	<0.001
OGIS (ml/min/m^2)	282±174	421±16	<0.001
CSI [10^{-4} min^{-1}/(μU/ml)]	1.7±0.24	4.0±0.81	0.015
AIR (pmol/L)	170±31	545±68	<0.001
Dispositionion Index	177±144	2148±675	0.011
GLP-1 response (pmol/L)	639±110	588±122	0.305
Incretin effect (%)	1.44±0.12	5.16±1.28	0.012

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1276-P

Nonalcoholic Fatty Liver Disease (NAFLD) in Hispanic Youth with Dysglycemia: Heightened Risk for Subclinical Atherosclerosis (ScA)

ANCA TOMSA, SARA KLINEPETER BARTZ, ZILI DAVID CHU, RAJESH KRISHNAMURTHY, RAMKUMAR KRISHNAMURTHY, ELIZABETH JOHNSON, SUSAN SHARMA, SARAH BARLOW, FIDA BACHA, *Houston, TX*

Obese Hispanic adolescents (OHA) are at high risk for both type 2 diabetes (T2D) and NAFLD. It is not clear if NAFLD confers an added risk for ScA in OHA with dysglycemia. We investigated endothelial function biomarkers of ScA in OHA with dysglycemia, with NAFLD (MRS hepatic fat fraction >5%) vs. without NAFLD. OHA (mean age: 15.2±0.4 years), 16 with prediabetes (PreD) and 10 with T2D underwent evaluation of reactive hyperemia index (RHI) and augmentation index (AIx) by peripheral arterial tonometry, blood pressure (BP), lipids, insulin sensitivity (IS) by hyperinsulinemic-euglycemic clamp, body composition by DXA, abdominal (AF) and hepatic fat (HF) by MRI/MRS. Results are Mean±SEM. The NAFLD vs. no-NAFLD groups did not differ in age, gender, BMI z-score (2.3±0.1 in both), glycemic status, HbA1c (5.6±0.1 vs. 5.8±0.1%), BP, % body fat or AF. The NAFLD group had higher HF, LDL-cholesterol (96.8±5.8 vs. 75.4±5.8 mg/dl), lower IS, lower RHI (vascular reactivity) and higher AIx (vascular stiffness) measures (Table). HF was inversely related to RHI (r=-0.5, p=0.03) and positively related to AIx (r=0.7, p=0.001) independent of IS, BP or LDL-cholesterol. In OHA with dysglycemia, presence of NAFLD is associated with worse endothelial function measures (RHI and AIx) suggesting heightened CVD risk. This highlights the need for early intervention in this high-risk group of youth.

Table.

	No-NAFLD (8M/2F; 6 PreD/ 4T2D)	NAFLD (7M/9F; 10 PreD/ 6T2D)	P-value
% Body Fat	37.1 ± 2.3	41.2 ± 1.3	0.1
Visceral adipose tissue (cm^2)	97.71 ± 9.8	100.9 ± 6.5	0.8
Intrahepatic Fat (%)	3.4 ± 0.5	10.3 ± 1.1	<0.001
ALT (IU/L)	27.4±4.5	72.7±11.5	0.006
Insulin Sensitivity (mg/min/kg per μU/ml)	2.2 ± 0.3	1.6 ± 0.2	0.04
RHI	1.7 ± 0.1	1.4 ± 0.06	0.01
AIx	-11.0± 2.0	-2.9 ± 1.6	0.005

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1277-P

Can Maternal Apo B Levels Predict Apo B Levels in Preschool Age Offspring?

VALERIA HIRSCHLER, KAREN OESTREICHER, MAXIMILIANO MARTIN, CLAUDIA MOLINARI, ELIANA BOTTA, FERNANDO BRITES, *Buenos Aires, Argentina*

Previous studies in adults showed that Apo B was a better marker for risk of cardiovascular disease (CVD) than LDL-C. As far as we know, there is no information about the association between Apo B levels in mothers and in their pre-school age offspring. The objective was to determine the association between Apo B levels in mothers and in their pre-school age offspring. Data were collected cross-sectionally from a kindergarten school in November 2015. BMI, waist circumference, lipids, Apo B, and Apo A levels were obtained in mothers and their offspring. High Apo B levels were considered when Apo B ≥ III quartile. Eighty-four children (42 males) aged 5.3 ± 1.6 y and their mothers aged 33.8 ± 7.2 y were examined. Nineteen (24.4%) children were overweight and 9 (11.5%) obese; whereas 27 (39.1%) mothers were overweight and 27 (39.1%) were obese. Children of mothers with Apo B ≥ III quartile had significantly higher values of z- BMI (1.2 vs. 0.4), waist circumference (58 vs. 55 cm), LDL-C (98 vs. 79 mg/dL), and Apo B (92.5 vs. 73.9 mg/dL) than those with maternal Apo B <III quartile. Multiple linear regression analysis showed that maternal Apo B levels were significantly associated with Apo B levels in their offspring adjusted for age, gender and children's z-BMI, and maternal BMI (Beta, 019; .p=0.03; R^2 0.25). Furthermore, multiple logistic regression analysis showed a significant increase in the odds ratio for high Apo B (≥ III quartile) among pre-school age children whose mothers had Apo B ≥ III quartile compared with those with maternal Apo B< III quartile adjusted for gender, age, and children's BMI [odds ratio (OR), 5.7; (95% CI 1.3-25.5]. In this cohort, an offspring born to a mother with high Apo

B levels had approximately six times the likelihood of having high Apo B independently of age, gender, and adiposity; suggesting that these pre-school age children are at higher risk for cardiovascular disease.

1278-P

Pharmacokinetics and Pharmacodynamics of Dapagliflozin in Children and Adolescents with Type 2 Diabetes Mellitus

GIRIDHAR S. TIRUCHERAI, FRANK LACRETA, FRAZ A. ISMAT, WEIFENG TANG, DAVID W. BOULTON, *Princeton, NJ, Gaithersburg, MD*

Globally, childhood obesity has increased dramatically and has contributed to the increasing prevalence of type 2 diabetes mellitus (T2DM) among children and adolescents. Currently, there are limited approved treatment options for this growing patient population. The pharmacokinetic/pharmacodynamics (PK/PD) and safety profiles of dapagliflozin (DAPA) were evaluated in this open-label, randomized, parallel-group, pediatric phase 1 study. Patients aged 10-17 years with T2DM were randomized to a single oral dose of DAPA. Individual patient PK parameters of DAPA and its 3-O-glucuronide metabolite were derived by noncompartmental analysis. Urinary glucose excretion (UGE), fasting plasma glucose (FPG), and ease of swallowing were also evaluated. A total of 24 patients (8 per dose group) received a single oral dose of DAPA 2.5, 5, or 10 mg. DAPA was rapidly absorbed after oral administration (median time to maximum plasma concentration ~1.5 h) and increases in systemic exposures to the parent drug and its metabolite appeared to be dose-proportional. Mean 24-h UGE increased in a dose-related manner (52.8, 62.4, and 89.0 g for the 2.5-, 5-, and 10-mg dose groups, respectively). Mean FPG concentrations were lower for all groups on day 2 (124.0, 119.4, and 119.0 mg/dL for 2.5-, 5-, and 10-mg dose groups) vs. predose on day 1 (146.2, 152.1, and 139.8 mg/dL for 2.5-, 5-, and 10-mg dose groups). Six patients (25%) experienced ≥1 adverse event (AE); however, there was no dose-related pattern. All AEs occurred only once and most were mild in intensity. Almost all patients (n=23; 95.8%) reported easy swallowing of the DAPA tablets. The PK/PD of DAPA in this pediatric population was similar to that observed in adults with T2DM, thereby supporting that the same DAPA dosage used in adults can be evaluated in future phase 3 pediatric efficacy and safety studies. (NCT01525238).

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1279-P

Reduced Deoxyhemoglobin Threshold in the Prefrontal Cortex during Exercise in Pediatric Obesity

BRIAN TRAN, ABRAHAM CHIU, ROBERT V. WARREN, LARISSA CHAU, MARGARET SCHNEIDER, PIETRO GALASSETTI, *Irvine, CA*

Neural control of volitional effort is increasingly considered a key determinant of exercise tolerance. During incremental exercise to exhaustion, the prefrontal cortex (PFC) switches from a steady state of deoxygenated blood levels (HbR) to a rapid increase in HbR until exercise termination. We report here alterations to the threshold at which HbR changes in obese (Ob) relative to nonobese (non-Ob) children.

We therefore studied a total of 51 children, aged 12-15 yrs (18 Ob, 97±1 BMI%; 33 non-Ob, 63±1 BMI%), identifying the HbR thresholds in response to incremental exercise, as measured non-invasively with Diffuse Optical Spectroscopy (DOS). A DOS probe was placed on the left forehead, and DOS measurements of HbR were obtained via continuous wave near-infrared spectroscopy systems (TRS 200 and pocket NIRS, Hamamatsu, Japan) as the children underwent an incremental exercise test until exhaustion on cycle-ergometer/metabolic cart system (Carefusion, U.S.). HbR thresholds were calculated via linear segmented regression. Comparisons were made using one-tailed, independent Student's *t*-tests.

The HbR threshold occurred in Ob at a ~ 10% lower absolute work-rate (watts, W) (91 ± 9 vs.103 ± 7W); the difference was significant when normalized to body weight (1.2 ± 0.19 vs.1.8 ± 0.1 W/kg body weight, Ob vs. non Ob, P<0.0001), and when expressed as VO2 at threshold (18 ± 1 vs. 25 ± 1 mlO2/kg body weight, Ob vs. non Ob, P<0.0001). DEXA-determined lean body mass was available in about half the subjects at time of submission; preliminary analysis however showed a strong trend towards significance of HbR threshold expressed as workrate/kg lean body mass (2.0 ± 0.2 vs.2.4 ± 0.1 W/kg lean body weight, Ob vs. non Ob, P=0.06).

Our cohort of Ob children experienced earlier HbR thresholds in incremental exercise vs. non-Ob children, consistent with the concept that altered HbR threshold are related to exercise tolerance, highlighting the PFC's potential role in the volitional control of exercise termination.

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1280-P

Effects of a Higher vs. Lower Protein Energy Restricted Diet on Parameters of the Metabolic Syndrome in Adolescents: A Randomized, Controlled Trial

JOHN W. APOLZAN, DANIEL S. HSIA, CORBY K. MARTIN, *Baton Rouge, LA*

The aim of this pilot study was to provide data on parameters of the metabolic syndrome following isocaloric lower vs. higher protein energy restricted diets in overweight and obese adolescents utilizing the U.S. Department of Agriculture (USDA) MyPlate nutrition guide. Thirty two, 12-17 year old adolescents with body mass index ≥ 85th percentile were recruited for a 12-week free-living weight loss intervention. Participants were randomized to either a lower protein group (15% of energy as protein and 60% of energy from carbohydrate) or a higher protein group (30% of energy as protein and 45% of energy from carbohydrate). Both diets restricted energy intake by 25%. Dietary counseling was based on the USDA MyPlate guidelines. Participants had a fasting blood draw, blood pressure, and anthropometric measurements at baseline and week 12. Participants were 75% female and 62.5% black. Mean (± SD) baseline age, body weight, and BMI z-score were 14.3 ± 1.5 y, 96.0 ± 21.9 kg, and 2.21 ± 0.48, respectively. No baseline or change from baseline group differences were found. Thus, groups were combined. Systolic blood pressure (-2.5 ± 5.4 mm Hg), total cholesterol (-9.9 ± 17.8 mg/dL), HDL cholesterol (-2.0 ± 4.3 mg/dL), and LDL cholesterol (-7.1 ± 15.1 mg/dL) decreased significantly following the intervention ($p < 0.05$). Waist circumference tended to decrease (-1.9 ± 4.6 cm; p=0.06). Diastolic blood pressure, triglycerides, glucose, insulin, and HOMA-IR did not change from baseline. A higher dietary protein diet was not more effective than a lower protein diet in reducing parameters of the metabolic syndrome in this cohort. Most changes in parameters of the metabolic syndrome were beneficial except for a small decline in HDL. Overall, an adolescent intervention based on the USDA MyPlate guidelines does improve most parameters of the metabolic syndrome.

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1281-P

Maternal Feeding Practices and Preschool Children at Risk for Obesity and Diabetes

RACHEL G. TABAK, CYNTHIA D. SCHWARZ, DEBRA HAIRE-JOSHU, *St. Louis, MO*

The Healthy Eating and Active Living Taught at Home (HEALTH) study tests the impact of a weight loss intervention on obese mothers at risk for diabetes and their preschool child at risk for obesity. These baseline data explore factors to determine whether maternal feeding practices are associated with perception of child weight status.

HEALTH enrolled 230 mothers (mean age 32 years, SD = 6; MN BMI =35; African American 31%) and their preschool child (MN BMI %= 81; MN age =3.4). Maternal feeding practices were self-reported using the modified 32 item Parent Feeding Questionnaire assessing: Difficult Child Feeding; Concern about Child Overeating or Overweight; Pushing Child to Eat; Food to Calm Child; Concern Child Is Underweight; Control of Feeding; Feeding Interactions; Age-Inappropriate Feeding. Maternal BMI and child BMI Z-scores were calculated from measured height and weight. Logistic regression and correlations explored associations between demographics, accuracy of child weight perception, and feeding practices.

Fifty-seven percent of mom's accurately estimated, 3% overestimated, and 40% underestimated their child's weight status. Concerns the child was overeating were positively correlated with BMI in the total sample (r=0.32, p<.001) and among moms accurately estimating child's weight (r=0.52, p<.001). Among mothers underestimating their child's weight, the child's BMI percentile was negatively correlated with pressuring the child to eat more (r=-0.30, p<.001) and concern about the child being underweight (r= -0.47, p<.001). There were no significant findings between maternal perceptions and other feeding practices.

Feeding practices appear to be influenced by maternal perception of their child's weight. This is particularly relevant as many mothers underestimate their child's risk for obesity. Diabetes prevention interventions should assess and impact maternal perceptions and feeding practices.

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1282-P

Effect of Exercise and High-Fat Feeding on Inflammatory Cytokines in Obese and Healthy Children

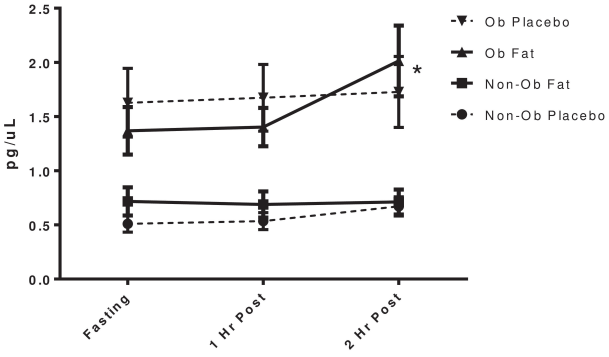
ABRAHAM S. CHIU, PETER HORVATH, HOANG PHAM, GOUTHAM GANESAN, FRANK ZALDIVAR, PIETRO GALASSETTI, *Irvine, CA*

Adult and childhood obesity is marked by chronic low-grade inflammation; reflected by altered circulating cytokine levels that modulate adaptive and

For author disclosure information, see page A696.

innate immune systems. We designed this study to compare the effects of two common pro-inflammatory stimuli, hyperlipidemia and exercise, on the same cohort of obese (Ob) children. Hyperlipidemia: 7 Ob (BMI ≥95%, 14±3 y.o., 3F) and 8 Non-Ob (13±2 y.o., 3F) children ingested either 1.5g fat/kg or a non-caloric placebo after an overnight fast. Blood was drawn at fasting, 1 h, and 2 h after ingestion. Exercise: the same children underwent 10 sets of 2 min cycling at 80% peak VO2 + 1 min rest. Plasma samples were taken at baseline, end exercise, and 1 h post for lipid panels, differential blood counts and ELISA assays of MCP-1, IL1-RA, IL-6. Data was analyzed via 2-way RM AVOVA + Dunnet's post-hoc test. IL-6 was significantly elevated, Ob vs. non-Ob, at all time points (p<.02-.001), and increased significantly over baseline, only in Ob, at 1 hr post-exe (+32±26%) and 2 h post fat feeding (+68±36%). IL-1RA was systematically elevated, Ob vs. non-Ob, (p<.05-.001) but unchanged by study stimuli. MCP-1 was similar across groups at baseline and similarly increased at end exercise. Pro-inflammatory cytokine signaling is increased in Ob children, with IL-6 appearing to be the most sensitive factor, possibly contributing to the long term pro-inflammatory modulation of cardiovascular risk.

Figure. Plasma IL-6 Concentrations.



Plasma IL-6 in obese (Ob) and non-obese (non-Ob) children at fasting, 1h, and 2h after ingestion of either a high-fat (1.5 g/kg) drink or a non-caloric placebo. At all time points, values in the Ob group were significantly elevated vs corresponding non-Ob values. * p<0.001 vs Fasting, Ob group, high-fat feeding

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1283-P

Readiness for Change among Indigenous Youth with Type 2 Diabetes

JONATHAN MCGAVOCK, ALLISON DART, KATELYN GOERTZEN, ANITA DURKSEN, CAITLIN MCFAYDEN, ELIZABETH SELLERS, BRANDY WICKLOW, ICARE INVESTIGATOR TEAM, *Winnipeg, MB, Canada*

Introduction: Behavioural lifestyle interventions have generally proven ineffective for improving cardiometabolic risk in youth with type 2 diabetes (T2D), possibly due to a lack of readiness for making lifestyle changes.

Hypothesis: We hypothesized that (1) Indigenous youth aged 10-18 years with T2D would display a lower readiness for change, compared to controls without T2D and (2) readiness for change would be associated with measures of cardiorenal risk.

Methods: We performed cross-sectional comparisons of readiness for change (Transtheoretical Model) for behaviour modification between Indigenous youth with T2D and matched controls. The main outcome measures were readiness for achieving daily targets for (1) physical activity; (2) fruit and vegetable intake; (3) saturated fat intake and (4) sedentary habits determined from validated questionnaires. Secondary outcomes were HbA1c, 24-hr blood pressure, BMI Z score and albumin to creatinine ratio (ACR).

Results: Youth with T2D (n=137) were younger (15.2 vs. 16.4 yrs; p=0.005) and had a lower BMI Z score (2.3 vs. 2.7, p=0.03) compared to controls (n=48). Youth with T2D were more likely to be in the action/maintenance stage of change for physical activity (27% vs. 13%, p=0.035) compared to controls, while no differences were observed in the readiness for daily fruit and vegetable intake (13% vs. 17%), sedentary habits (42% vs. 38%); or saturated fat intake (44% vs. 30%,). Only 5 youth with T2D were in the action/maintenance phase for all 4 behaviours and 48 were in the action/maintenance phase for 2 or 3 behaviours. Youth with T2D in the action/maintenance phase for all 4 behaviours (n=5) displayed a lower HbA1c (6.5 ± 1.1 vs. 9.8 ± 2.6%; p=0.001) and ACR (0.5 ± 0.8 vs. 5.5 ± 6.8, p=0.001), without differences in blood pressure or BMI Z score compared to youth in not in the action phase of behaviour change.

Conclusion: Readiness for behaviour change is low among Indigenous youth with T2D. Youth in the action/maintenance stage of change had better glycemic control and less proteinuria.

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1284-P

Improving Body Composition and Metabolic Profile among Southwestern Native American Children to Reduce the Burden of Diabetes

VALLABH SHAH, PHILLIP SANDY, DONICA GHAHATE, JEANETTE BOBELU, LESLIE COLIP, MARK R. BURGE, *Albuquerque, NM*

Native Americans are at higher risk for becoming obese and suffering from obesity-related illness compared to others. Also, prevention methods may not be successful with this group, and intervention attempts aimed at children are sparse in the literature. We evaluated the effectiveness of 24 weeks of physical fitness with nutritional counseling in children aged 11-17 years on various metabolic parameters and body composition.

Native American adolescents (n=66) aged 13.7±1.7 years participated in an exercise program 3 times a week for 60 minutes of dietary instruction, aerobic exercise, and resistance training. Parents attended an instructional session on healthy eating and the preparation of nutritional lunches. Body composition as measured by bioelectrical impedance and metabolic parameters were assessed at baseline, 12 weeks, and 24 weeks.

Only 32 subjects completed all three visits; 19 males and 14 females. Participants in the fitness program showed significant improvements in A1c (5.9±0.7 vs. 5.6±0.5%), LDL cholesterol (97±20 vs. 79±17 mg/dl), and triglyceride levels (172±89 vs. 106±47 mg/dl). At baseline, 13 subjects were non-DM, 15 had pre-DM, 2 had DM, and 2 were unclassified using A1c criteria. At week 24, 19 subjects were non-DM, 11 had pre-DM, 1 had DM, and 1 was unclassified using A1c criteria. We also found significant improvements in BMI percentile (95±10 vs. 92±12), total body fat (28.1±8 vs. 26.0±9%) and free fat mass (71.8±8 vs. 74.1±9%) at 24 weeks.

A standardized fitness program among Native American children was effective at reducing A1c, fasting glucose and lipids, and improving body composition, thereby reducing the burden of diabetes over the course of 6 months.

Supported By: National Institutes of Health

1285-P

Comparison of the Exposure-Response Relationship of Dapagliflozin in Adult and Pediatric Patients with Type 2 Diabetes Mellitus

JOANNA PARKINSON, WEIFENG TANG, CARL-CHRISTER JOHANSSON, DAVID W. BOULTON, BENGT HAMRÉN, *Mölndal, Sweden, Gaithersburg, MD*

The prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents has increased in the United States. Despite this growing population, there are currently limited approved treatments for pediatric patients with T2DM. A pharmacometric modeling approach was taken to quantitatively assess the exposure-response (E-R) relationship of dapagliflozin (DAPA) in adult and pediatric patients with T2DM and identify potential sources of variability. Data were integrated from 2 adult and 1 pediatric studies of single-dose, orally administered DAPA. Data from 63 predominantly white or Asian (92.4%) adult and 20 pediatric (45.8% white; 45.8% black) patients were included. The relationship between DAPA exposure (area under the concentration-time curve) and response (24-h urinary glucose excretion [UGE)] was adequately described by a sigmoidal maximal effect model. Model-predicted UGE response was higher in pediatric (47.4, 67.5, and 85.9 g/24 h for 2.5-, 5-, and 10-mg dose groups) than in adult (31.2, 43.5, and 54.3 g/24 h for 2.5-, 5-, and 10-mg dose groups) patients. Baseline FPG, estimated glomerular filtration rate, and sex were identified as significant covariates in both populations, while race was identified as a significant covariate in pediatric patients only. In summary, after accounting for significant covariates, adult and pediatric patients with T2DM administered a single oral dose of DAPA had similar E-R relationships. The difference in UGE response is likely associated with differences in covariates between the 2 populations; however, interpretation may be limited by small sample size and racial disparity. Overall, these results support that the same DAPA dosage used in adults with T2DM be evaluated in future phase 3 efficacy and safety studies in pediatric patients with T2DM. (NCT00162305, NCT00538174, NCT01525238).

Supported By: AstraZeneca

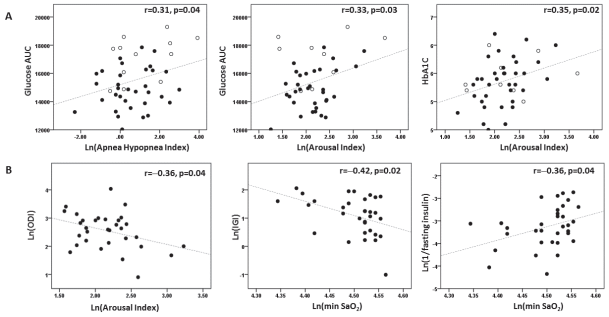
1286-P

Sleep Apnea and Arousals Are Associated with Glycemic Markers of Risk for Type 2 Diabetes (T2D) in Obese Adolescents

TAMARA S. HANNON, SARA E. WATSON, HASNAA E. JALOU, SANGEETA CHAKRAVORTY, SILVA A. ARSLANIAN, *Indianapolis, IN, Louisville, KY, Pittsburgh, PA*

We investigated relationships between obstructive sleep apnea (OSA) and oral glucose tolerance test (OGTT) indices of glycemia and β-cell function. We hypothesized OSA, measured by the apnea-hypopnea index (AHI) during polysomnogram (PSG) is associated with dysglycemia and lower β-cell function (oral disposition index, ODI). The study included 47 adolescents 12-18 y; 42 with complete OGTT and PSG data. PSGs were performed the night preceding or following the OGTT. ODI was calculated as the product of insulinogenic index (IGI) and 1/fasting insulin. Nonparametric data were log transformed; Pearson correlation coefficients were calculated. Twelve participants had prediabetes; 35 had normal glucose tolerance (NGT). The median AHI was 2 (0-50) events/hour. AHI and arousals were associated with glucose area under the curve; arousals with HbA1c (Figure, Row A, open circles=prediabetes; closed circles=NGT). Sleep parameters were not associated with 1/fasting insulin, IGI or ODI. When NGT and prediabetes groups were analyzed separately, arousals were associated with ODI; minimum oxyhemoglobin saturation with IGI and 1/fasting insulin only in those with NGT (Figure, Row B). In obese adolescents sleep apnea and arousals are associated with higher glycemia during OGTT. It remains to be determined if treating OSA will be associated with improvements in glycemia.

Figure.



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1287-P

Insulin Secretion, but Not Insulin Sensitivity, Is Associated with Decreased SHBG during Puberty

MEGAN M. KELSEY, DONNA JIN, ALLISON HILKIN, LAURA PYLE, RACHAEL VAN PELT, KRISTEN J. NADEAU, PHILIP S. ZEITLER, *Aurora, CO, New York, NY*

Puberty is associated with transient, physiologic insulin resistance. These changes appear to place obese youth at risk for becoming metabolically unhealthy and developing type 2 diabetes (T2D), although mechanisms are unclear. We previously reported that leptin and insulin-like growth factor-1 (IGF-1), but not sex hormone binding globulin (SHBG), are associated with insulin sensitivity (Si), independent of body mass index (BMI), in lean and obese early pubertal youth. As progression to T2D is ultimately due to decreased insulin secretion, the goal of the current study was to evaluate factors related to first phase insulin secretion (AIRg) in early pubertal youth.

Methods: Lean (n=44) and obese (n=46) early pubertal (Tanner 2-3) youth had AIRg evaluated by an IV glucose tolerance test. Univariate regression assessed potential predictors of AIRg early in puberty, adjusted for race/ethnicity and BMI z-score. Variables assessed included: fasting lipid panel, dehydroepiandrosterone-sulfate, estradiol, total testosterone, adiponectin, leptin, IGF-1, SHBG, waist circumference, % body fat (by DXA), C-reactive protein, physical activity (PA, by questionnaire) and free androgen index. Stepwise selection identified factors that best predict AIRg.

Results: Leptin (R^2=0.67, p=0.007), IGF-1 (R^2=0.59, p=0.02) and PA (R^2=0.63, p=0.02) were all significant predictors of AIRg, in univariate analyses. Using stepwise selection, only leptin (2.2% change/1 unit increase in AIRg, p<0.0001) and SHBG (-1.0% change/1 unit increase in AIRg, p=0.005) were independent predictors of AIRg.

Conclusions: AIRg, but not Si, is independently associated with SHBG during puberty. This may support previous in vitro studies showing insulin suppression of hepatic SHBG production. Further research on the bi-directional interaction between changes in sex steroids and glucose metabolism during puberty in lean and obese youth will inform our understanding of the pathophysiology of T2D in at-risk youth.

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PEDIATRICS—TYPE 1 DIABETES

Moderated Poster Discussion: Novel Insights into Pediatric Type 1 Diabetes *(Posters: 1288-P to 1295-P), see page 21.*

1288-P

Elevations in the Fasting Serum Proinsulin: C-Peptide Ratio Precede the Onset of Type 1 Diabetes

EMILY K. SIMS, ZUNAIRA CHAUDHRY, RENECIA WATKINS, FAROOQ SYED, JANICE BLUM, FANQIAN OUYANG, SUSAN PERKINS, RAGHAVENDRA G. MIRMIRA, JAY M. SOSENKO, LINDA A. DIMEGLIO, CARMELLA EVANS-MOLINA, *Indianapolis, IN, Miami, FL*

Type 1 diabetes (T1D) is classically defined as autoimmune destruction of the pancreatic β-cell. However, recent data suggest cell-intrinsic stress, such as endoplasmic reticulum (ER) stress may precede and/or contribute to the autoimmune process. We tested whether an elevation in the serum proinsulin/C-peptide (PI:C) ratio, a biomarker of β-cell endoplasmic reticulum (ER) dysfunction, was associated with progression to type 1 diabetes. Fasting total proinsulin and C-peptide levels were measured in banked serum samples obtained from TrialNet Pathway to Prevention (PTP) participants, a cohort of autoantibody positive nondiabetic relatives of individuals with type 1 diabetes. Samples were obtained approximately 12 months before diabetes onset from PTP progressors who developed diabetes (n=60); and compared to age, gender, and BMI-matched nonprogressors who remained normoglycemic (n=58). PI:C ratios were calculated as molar ratios and multiplied by 100% to obtain proinsulin as a percentage of C-peptide.

Although absolute proinsulin levels did not differ between groups, PI:C ratios were significantly increased in antibody-positive subjects who progressed to diabetes compared to nonprogressors (median of 1.81% vs. 1.17%, p=0.03). The difference between groups was most pronounced in subjects ≤10 years old, where progressor PI:C ratios were nearly triple those of nonprogressors; 90.0% of subjects in this age group in the upper PI:C quartile progressed to develop diabetes. Logistic regression analysis, adjusted for age and BMI, demonstrated increased odds of progression for higher lnPI:C (natural log PI:C) values (odds ratio =1.44, confidence interval: 1.02, 2.05). These data suggest that β-cell ER dysfunction precedes type 1 diabetes onset, especially in younger children. Elevations in the serum PI:C ratio may have utility in predicting the onset of type 1 diabetes in the presymptomatic phase.

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1289-P

Prevalence and Management of Patients with Type 1 Diabetes and Autism Spectrum Disorder

KELLY STANEK, JENNIFER K. RAYMOND, SHIDEH MAJIDI, *La Mirada, CA, Aurora, CO*

There is limited research on the prevalence of both type 1 diabetes (T1D) and Autism Spectrum Disorder (ASD). Whether there is an increased risk of ASD in T1D compared to in the general population is unclear. Additionally, there is no research on characteristics of patients with both T1D and ASD. We investigated the prevalence of ASD in a large diabetes center as well as described the diabetes characteristics and management in those with ASD and T1D. Of 2610 patients aged 18 months to 18 years with T1D, 30 (28 male, 2 female) also had a diagnosis of ASD, a prevalence rate of 1 in 87 (1.15%). This is similar to the prevalence of ASD in Colorado, ~1 in 85 (1.18%). Those with ASD and T1D were an average age of 12.9 years and had diabetes for 5.0 years. Compared to the T1D patient population, those with ASD and T1D appear to have similar hemoglobin A1c (HbA1c) and blood glucose tests per day, but appear less likely to be on an insulin pump. Overall, prevalence of ASD in this pediatric T1D population is similar to the prevalence of ASD in the general Colorado pediatric population. T1D management is similar between the two populations, except for insulin regimen, which indicates similar glycemic control and adherence behaviors are possible in both

For author disclosure information, see page A696.

populations. Further research is being done to identify unique challenges, and potential strategies to overcome them, to help providers and families provide optimal diabetes care to this population.

Table.

	ASD+T1D (n=30)	T1D (n=2330)
Sex (%Female)	6.7%	47.8%
Race/Ethnicity (%): non-Hispanic white; Hispanic; Other	83.3% non-Hispanic white; 3.3% Hispanic; 13.3% Other	72.0% (n=1574) non-Hispanic white; 16.6% (n=358) Hispanic; 10.3% (n=223) Other
Duration of Diabetes (years)	5.0±3.1	5.0±3.7
HbA1c (%)	8.2±1.5	8.8±1.8
Blood Glucose Tests (per day)	5.6±2.4	5.2±2.7
Insulin Regimen (%): Multiple Daily Injection (MDI); Insulin Pump; NPH	56.7% MDI; 43.3% Insulin Pump; 0.0% NPH	43.0% (n=677) MDI; 56.8% (n=894) Insulin Pump; 0.19% (n=3) NPH

Supported By: National Institutes of Health

1290-P

Correction of Treg Activation Defect in Type 1 Diabetic Children and Adults with In Vitro TNFR2 Agonism

YOSHIAKI OKUBO, HEATHER TORREY, JOHN BUTTERWORTH, HUI ZHENG, DENISE L. FAUSTMAN, *Boston, MA*

Tumor necrosis factor receptor 2 (TNFR2) is obligatory for induction, maintenance and expansion of activated regulatory T cells (aTregs), which are known to prevent or halt various forms of autoimmunity in animal models and humans. In this study, we show that although type 1 diabetics (T1D) have normal numbers of total Tregs, they have an increase in resting Tregs (rTregs) and a decrease in aTregs (defined by CD45 protein) compared to controls (n=55 T1D, n=45 controls, p=0.01). A large cross-sectional study of children and adults with T1D reveals that this Treg activation defect is lifelong (n=100 T1D, p<0.01). Lower numbers of aTregs were associated with having less residual C-peptide secretion from the pancreas (p=0.08) and poorer HbA1c control (p=0.03). Using two separate *in vitro* Treg expansion protocols, TNFR2 antibody agonism corrected the T1D activation defect by triggering conversion of rTregs into aTregs (n=54 T1D, p<0.001). TNFR2 antibody agonism was superior to standard protocols of Treg expansion and superior to tumor necrosis factor (TNF) in expanding the most potent subsets of Tregs. TNFR2 antibody expansion protocols exclusively expanded Treg cells but not CD4 T cells, thus creating homogenous populations of potent human Tregs in culture. In T1D, TNFR2 agonist-expanded Tregs were functionally potent by virtue of suppressing autologous cytotoxic T cells in a dose-dependent manner compared to controls. Targeting the TNFR2 receptor for Treg expansion *in vitro* and perhaps *in vivo* may be a means to correct the Treg activation defect in T1D children and adults.

1291-P

NADPH-derived Superoxide Influences CD4 T Cell Activation by Oxidizing Membrane Thiols Levels

NADINE N. MORGAN, HUBERT M. TSE, *Birmingham, AL*

Reactive oxygen species (ROS) have been shown to play a role in mediating T cell autoreactivity in the development of autoimmune diseases including type 1 diabetes (T1D). It was recently shown that redox regulation of cell surface thiol levels can influence T cell activation, and the development of autoimmunity. An increase in the number of reduced cell surface thiols on arthritogenic CD4 T cells contributed to exacerbated susceptibility in developing autoimmune arthritis. Our goal is to determine mechanistically whether NAPDH (NOX)-derived superoxide can modulate the oxidation status of cell surface thiols on diabetogenic CD4 T cells and thereby influence T cell effector responses. To test this hypothesis, we utilized the NOD.BDC-6.9.Ncf1^{m1J} TCR transgenic mouse that possesses superoxide-deficient CD4 T cells that recognize the putative autoantigen, islet amyloid polypeptide. BDC-6.9.Ncf1^{m1J} CD4 T cells stimulated with their cognate BDC-6.9 hybrid peptide displayed a 3.5- and 1.5-fold increase in IFN-γ and TNF-α production, respectively, in comparison to NOX-sufficient BDC-6.9 CD4 T cells. Corroborating the increase in Th1 effector cytokine synthesis, hybrid peptide-stimulated BDC-6.9.Ncf1^{m1J} CD4 T cells displayed a 1.8-fold increase in the percentage of CD25 and a 1.5-fold increase in the percentage of CD69, classical T cell activation markers, in comparison to BDC-6.9 T cells. To correlate the increase in T cell activation, we examined the number of reduced cell surface thiols on CD4 T cells using Alexa Fluor 647 coupled with maleimide. Interestingly, hybrid peptide stimulated BDC-6.9.Ncf1^{m1J} CD4 T cells exhibited a 2.3-fold increase in the percentage of reduced cell surface thiols in comparison to stimulated BDC-6.9 CD4 T cells. Overall, our data indicates that NOX-derived superoxide mediates the oxidation status of T cell surface thiols to influence diabetogenic CD4 T cell effector responses.

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1292-P

Variations in the Relationship between Glucose and HbA1c May Contribute to Clinic and Country Differences in HbA1c

ANNA RYDIN, KRISTIN LUNDQVIST, MARIE EKSTRÖM, RAGNAR HANAS, *Uddevalla, Sweden*

In Sweden and other countries there is a large range between clinics in mean HbA1c. Our aim was to investigate if this range is influenced by variation of the relationship between mean glucose levels and HbA1c. Mean glucose over 7, 14 and 30 days was collected with blood glucose (BG) tests, Continuous Glucose Monitoring (CGM) and Flash Libre (FGM). Patients were included if over 1 month > 8 BG tests/day or CGM/FGM >30% of the day was registered. We calculated mean, median, standard deviation (SD), Coefficient of Variation (CV) and Mean Absolute Difference (MAD) for glucose and HbA1c. 59 patients with type 1 diabetes were included: age 11.6±4.0 years, diabetes duration 4.6±2.9 years and HbA1c 52.2±10.3 mmol/mol (6.9±0.9%). 2 patients were of non-Swedish origin. Correlations between glucose over 30 days and HbA1c was: BG: r=0.75, CGM: r=0.70 and Libre: r=0.93; all p< 0.001. The variation as SD, CV and MAD was similar to that of HbA1c for all types of glucose measures. The relationship between mean glucose levels, CGM (n=25) or FGM (n=20) when available, otherwise BG (n=14), and HbA1c in a linear regression equation was: HbA1c (mmol/mol) =11.94+ (4.58 x glucose [mmol/l)], r=0.82, p<0.001. When plotting with published data (Wilson 2008, Nathan 2008), the regression equation had a different slope, which may influence HbA1c comparisons. However, all 3 regression lines met in the area of 50-60 mmol/mol (6.7-7.6%), in line with national and international HbA1c targets (NICE <48 mmol/mol, 6.5%, Sweden <52 mmol/mol, 6.9%, ADA and ISPAD <58 mmol/mol, 7.5%). There seems to be no difference in the variation of mean glucose levels and HbA1c in our clinic with a very homogenous ethnic background. However, Swedish children seem to get lower HbA1c for the same blood glucose levels compared to data from populations with mixed ethnicity. This can be of importance for HbA1c comparisons between clinics and countries. Comparing percentage of patients below target HbA1c may be a better measure than mean HbA1c.

1293-P

When School Doesn't Make a Difference: Glycemic Control in Pediatric Participants Based on Time of Year

JENNIFER L. SHERR, CLAIRE T. BOYLE, KELLEE M. MILLER, ROY W. BECK, WILLIAM V. TAMBORLANE, *New Haven, CT, Tampa, FL*

Seasonal variation in glycemic control has been postulated to occur in school age children with T1D, as summer vacation months often lack structure. To address this question, data from 1,972 pediatric participants from 56 centers participating in the T1D Exchange Registry were utilized. To be included, subjects had to be age 8 to <18 yrs, have a duration of T1D >3 yrs (to minimize the influence of changes in residual endogenous insulin secretion over time), and have an HbA1c measurement in each of three pre-defined time periods: prior to start of summer vacation (March, April, May), end of summer vacation (August and September), and back in school (November and December). Mean participant age was 13±3 years and mean duration of diabetes was 7.4±2.8 yrs (range 4-17 yrs). Across the cohort, no difference in HbA1c was observed before (8.5±1.3), during (8.5±1.3), or after (8.5±1.3) summer vacation overall and after stratifying by age, gender, and region. Only about 19% of patients met an HbA1c target of <7.5% within each time period. These data do not support the conventional wisdom that the changes in activity patterns and mealtimes during summer vacation are associated with a worsening of metabolic control in school-aged children with T1D. Instead, they highlight the need for improving control in most youngsters throughout the year.

Table. Seasonal HbA1c Averages by Demographic Characteristics.

	Prior to Start of Summer Vacation (mean±SD)	End of Summer Vacation (mean±SD)	Back in School (mean±SD)	p-value
Age (years)				
8-<13	8.2±1.0	8.3±1.1	8.2±1.0	0.60
13-<18	8.7±1.4	8.7±1.5	8.7±1.4	0.12
Gender				
Female	8.6±1.3	8.5±1.3	8.5±1.3	0.60
Male	8.5±1.3	8.5±1.3	8.5±1.3	0.59
Race/ethnicity				
White non-Hispanic	8.4±1.2	8.4±1.3	8.4±1.2	0.61
Other	9.0±1.5	8.8±1.5	8.9±1.5	0.48
Region				
Midwest	8.6±1.2	8.6±1.3	8.6±1.2	0.63
Northeast	8.5±1.3	8.5±1.3	8.4±1.3	0.85
South	8.6±1.3	8.6±1.3	8.7±1.4	0.74
West	8.5±1.3	8.5±1.4	8.5±1.3	0.43

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Clinical Diabetes/ Therapeutics **POSTERS**

1294-P

Unique Characteristics of Hispanic Youth with New Onset Type 1 Diabetes

KAJAL GANDHI, MARIA J. REDONDO, *Houston, TX*

There is evidence that type 1 diabetes (T1D) is a heterogeneous disease in its ethiopathogenesis/clinical course. Possibly due to the higher frequency of T1D in non-Hispanic white (NHW) children, studies in racial/ethnic minorities are lacking. To gain insight into the contribution of ethnicity to T1D heterogeneity, we studied demographic/clinical characteristics in Hispanic (Hisp) children with new onset T1D.

We analyzed a cross-sectional, hospital-based series of 709 children with new onset T1D (clinical diagnosis with exclusion of both negative islet autoantibodies and obesity, i.e., BMI >=95th age and sex-adjusted percentile). Mean [SD] age was 9.7 years [4.4], c-peptide 0.63 ng/ml [0.93], and age- and sex-adjusted BMI percentile 69.3 [25.5]. 52% were males, 58.6% NHW, 21% Hisp, 15.4% black, 4.9% other. Demographic and clinical variables were analyzed. P-values <0.05 were considered significant.

Hisp youth had greater random C-peptide at diagnosis (mean 0.81 ng/ml, SD 1.63) and higher BMI percentile (mean 74.9, SD 25) than non-Hisp youth (respectively, mean 0.59 ng/ml, SD 0.63, p=0.01; and mean 67.8, SD 1.17, p=0.006). Hisp children were also more likely to present in cold months (September-February) (65.5%) compared to non-Hisp children (55.6%, p=0.032). By multivariate analysis, younger age of onset, higher c-peptide at onset and presentation during cold months were independently associated with Hisp ethnicity after controlling for BMI percentile (p<0.0012). There were no differences for sex, diabetic ketoacidosis, type and number of islet autoantibodies, hemoglobin A1c or glucose at onset.

At onset of T1D, compared to other ethnicities, Hisp youth are more likely to present during colder months, at a younger age and with greater c-peptide, after adjustment for BMI percentile. These findings suggest that ethnicity may contribute to heterogeneity of T1D pathogenesis with significant implications for intervention.

1295-P

Insulin Patch Pump Therapy vs. Multiple Daily Injections (MDI) in 2,729 Youth with Type 1 Diabetes (T1D): Data from the German-Austrian DPV-Registry

THOMAS DANNE, BETTINA HEIDTMANN, BIRGIT RAMI-MERHAR, RALPH ZIEGLER, REINHARD W. HOLL, *Hannover, Germany, Hamburg, Germany, Vienna, Austria, Münster, Germany, Ulm, Germany*

The OmniPod$^{(R)}$ Insulin Management System (Insulet Corporation, Billerica, MA) is a tubeless insulin pump with the second generation becoming available in Germany and Austria in 2012. To analyse the effect of switching to patch-pump insulin delivery, those 229 centers from the DPV-diabetes registry database using this patch pump between 2012 and 2015 were searched for T1D patients with data 1 year prior to switch plus a 1 year follow-up period and matched with MDI patients from the same center. In 2729 patients [536 OmniPod, 2193 MDI; age: 12.4 ± 3.9, diabetes duration: 4.1 ± 3.6 (years, mean ± SD)] the patch pump patients compared to those remaining on MDI showed a significant initial improvement in HbA1c (expressed in relation to the DCCT-normal range) and a lower total daily dose of insulin after the switch to OmniPod therapy (Table, *statistical significance adjusted for age, diabetes duration, gender, baseline difference). The raw Standard Deviation Score (SDS) of BMI was similar, but slightly higher after demographic adjustment in patients using patch pumps. Although registry data is unable to show superiority or inferiority of one mode of therapy to another, switching to patch pump therapy appears as an effective alternative to MDI in youth with T1D.

Table. Comparison of MDI and Patch Pump Patients from Centers with at Least 10 Patch Pump Patients.

Parameter	Treatment	N	Year Prior Switch	1 Year Later	Significance* (PP vs. MDI)
HbA1c [%]	Patch Pump (PP)	536	7.5 ± 1.1	7.4 ± 1.0	p<0.001
	matched MDI	2193	7.7 ± 1.3	7.8 ± 1.3	
Insulin dose [U/kg/24h]	Patch Pump		0.79 ± 0.28	0.77 ± 0.34	p<0.001
	matched MDI		0.86 ± 0.31	0.90 ± 0.30	
Body Mass Index [SDS]	Patch Pump		0.40 ± 0.92	0.48 ± 0.87	p<0.02
	matched MDI		0.43 ± 0.92	0.48 ± 0.93	

Supported By: Insulet Corporation

Moderated Poster Discussion: Advances in Pediatric Type 1 Diabetes *(Posters: 1296-P to 1303-P), see page 20.*

1296-P

Dapagliflozin Lowers Insulin Requirement Independent from Baseline A1c in Youth with Type 1 Diabetes

TORBEN BIESTER, MARYAM FATH, BAERBEL ASCHEMEIER, MARCEL FREY, MARCUS F. SCHEERER, OLGA KORDONOURI, THOMAS DANNE, *Hannover, Germany, Giessen, Germany, Wedel, Germany*

Youth with type 1 diabetes (T1D) infrequently achieve A1c targets. This is the first study to assess the safety, tolerability, and pharmacokinetics of a SGLT2 inhibitor as add on to insulin in relationship to A1c in youth. In a placebo-controlled, randomized, crossover study, the effect of a single dose of 10mg dapagliflozin (DAPA) on the insulin dose administered i.v. during a glucose-infusion for the ensuing 24 hours with blood glucose kept between 160 - 220 mg/dl was studied in 33 youth (14 males, age: 16 (12-21) [median (range) years], diabetes duration 8 years (2-16)), stratified according to glycemic control being within target (n=11, A1c 5.5 to 7.4%), moderately elevated (n=11, 7.5 - 9.0%) or clearly elevated (n=11, 9.1 - 12.5%) (DCA, Siemens). DAPA reduced mean i.v. insulin dose by 13.6% (Table 1; P<0.0001 by ANOVA), irrespective of baseline A1c. Urinary glucose excretion was A1c-independently increased by 610% (Table 1; P<0.0001). 6 independent episodes in 6 patients with plasma β-hydroxybutyrate levels between ≥0.6 and <1.0 mmol/l have been observed after a liquid meal challenge, 5 episodes in the DAPA and 1 in the placebo group. In youth with T1D, DAPA led to a significant reduction of insulin needed to achieve target glucose irrespective of preexisting A1c levels. This study provides a proof of concept for adjunct SGLT2 inhibitor therapy in this age group.

Table 1. Pooled Analyses Over All A1c Subgroups.

Parameter	Treatment	N	Mean	STD	P-Value (ANOVA)
Insulin dose [U/kg/24h]	Dapaglifozin	33	0.92	0.2	<0.0001
	Placebo	31	1.10	0.2	
Urinary Glucose Excretion [g/24h]	Dapaglifozin	31	143.4	56.9	<0.0001
	Placebo	31	22.4	11.3	

Supported By: AstraZeneca

1297-P

Healthcare Utilization for Publicly Insured Children with Type 1 Diabetes in Florida and Texas

ASHBY F. WALKER, RONNY A. BELL, HEATHER L. MORRIS, MICHAEL J. HALLER, JON SHUSTER, BETSY SHENKMAN, YIJUN SUN, DESMOND SCHATZ, *Gainesville, FL, Winston-Salem, NC*

Studies documenting disparate outcomes in type 1 diabetes (T1D) according to socioeconomic and race/ethnic minority status often rely on cohorts from pediatric endocrine clinic databases, which may underrepresent children at greatest risk. This study used enrollment and claims data for children ages 0-9 in Florida and Texas with a diagnosis of T1D (inclusion criteria: ICD9 codes and insulin claims) in Medicaid and CHIP programs during 2013 (*N*=1,424). Rates of utilization (PCP visits and routine endocrinology visits using rendering provider taxonomies; diabetes ER visits and diabetes inpatient visits) were compared by age, gender, race/ethnicity, and census tract poverty level. Ordinal variables were analyzed by the Kruskal-Wallis test, nominal variables by Pearson's chi-square. Demographics: mean age of 6.7 (±2.04); 51% female; 32% Hispanic, 28% white, 11% black, 3% "other," and 27% "unknown." Only 27% met recommendations for routine visits to endo-

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

crinologists (4 times a year), 24% had only 1-2 visits and 5% no visits despite services being covered. Hispanic children had the highest rates of use for PCPs, routine endocrinology, and highest poverty risk (P<.001, Table 1). These findings show underuse of endocrinologists, especially for non-Hispanic blacks. More research is needed to understand barriers for publicly insured T1D children and to explicate associated consequences to health outcomes.

Table 1. TID Healthcare Utilization Rates by Race/Ethnicity in Texas and Florida. (*N*=1,424; 635 from FL and 789 from TX).

Variable	3-way comparison	Black vs. White	Black vs. Hispanic*	White vs. Hispanic*
Gender				
Male (n=471)				
Female (n=525)	0.51			
Census Tract Level Poverty Rate				
0-4.9% (n=55)				
5-9.9% (n=98)				
10-19.9% (n=223)				
20-39.9% (n=181)				
≥ 40% (n=38)	<.001**	0.03*	0.03*	<.001**
Number of (diabetic) visits to the Emergency Room				
0 Visits (n=864)				
1 Visit (n=108)				
2+ Visits (n=24)	0.55			
Number of (diabetic) inpatient Visits				
0 Visits (n=807)				
1 Visit (n=181)				
2+ Visits (n=8)	0.14			
Number of visits with a PCP				
≤2 Visits (n=263)				
3-5 Visits (n=353)				
≥6 Visits (n=380)	<.001**	0.95	<.001**	<.001**
Number of routine visits with an Endocrinologist				
0 Visits (n=42)				
1-2 Visits (n=348)				
3-4 Visits (n=285)				
5+ Visits (n=95)	0.03*	0.21	0.01*	0.10

*P<.05, **P<.001
Pearson's Chi-Square Test used for nominal variables and Kruskal-Wallis Test for ordinal variables
**Hispanic group had a higher rate than comparison group*

1298-P

Relationship between Mental Health (MH) and Glycemic Variability in Youth with T1D

KARA R. HARRINGTON, WILLIAM J. MCMULLEN, LISA VOLKENING, ANITA L. KAO, MICHELLE L. KATZ, LORI M. LAFFEL, *Boston, MA*

CGM offers a new dimension to explore associations between MH variables and physiological measures of glycemia. Glycemic variability was assessed in 120 youth (51% male; age 12.7±2.7 y [range 8-17]; T1D duration 6.1±3.6 y; A1c 8.0±0.1%; 84% pump use) who received CGM for 1 year. Variability was measured as the mean coefficient of variation (CV) of aggregated CGM data derived from 3 time points over the year [higher CV, greater variability]. Youth self-reported on 3 MH constructs; trait anxiety assessed with the State-Trait Anxiety Inventory (STAI-T); depression with the Center for Epidemiological Studies-Depression Scale for Children (CES-DC); fear of hypoglycemia (FOH) with the FOH Survey-Worry subscale (FOH-W). Higher survey scores indicate greater emotional distress. Annualized CGM use was the mean number of hrs/wk of CGM use during the year (89.3±45.7, range 0-156.1 hrs/wk). CV was 39±6% (range 24-58%); STAI-T 28±7 (range 20-60); CES-DC 10±9 (range 0-44); FOH 25±20 (range 0-93). CV did not vary by CGM use or A1c. All 3 MH measures were negatively correlated with CV (r=-.19 to -.20, all p≤.04). As the 3 MH measures were intercorrelated, separate multivariate models assessed their associations with CV. All MH measures were indirect significant predictors of CV while A1c and CGM use were not (Table). Youth prone to MH issues may experience less glycemic variability; future research can assess causes of this reduced variability.

Table. Multivariate Regression Models Predicting Glycemic Variability.

	R2		β	p-value
Model 1-anxiety	.07	A1c/CGM wear	-.008/-.0002	.13/.10
	p=.03	Trait anxiety	-.001	.01
Model 2-depression	.06	A1c/CGM wear	-.006/-.0001	.31/.13
	p=.07	Depression	-.0009	.04
Model 3-FOH	.07	A1c/CGM wear	-.008/-.0001	.14/.09
	p=.04	FOH	-.0005	.02

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1299-P

The Association of C-Peptide with BMI at the Diagnosis of Type 1 Diabetes (T1D) in Children Participating in the Diabetes Prevention Trial-Type 1 (DPT-1)

JAY M. SOSENKO, CARMELLA EVANS-MOLINA, LINDA A. DIMEGLIO, LISA E. RAFKIN, YUK-FUN LIU, JAY S. SKYLER, JERRY P. PALMER, *Miami, FL, Indianapolis, IN, London, United Kingdom, Seattle, WA*

Since C-peptide is used to estimate residual β-cell function at the diagnosis of T1D, we assessed whether BMI might influence specific C-peptide indices at diagnosis in autoantibody positive children. There were 98 children who progressed to T1D before 18.0 years of age (mean±SD age at diagnosis: 11.3±3.3 years) with 2-hr OGTTs and BMI measurements at diagnosis in DPT-1. The BMI z-score (BMIZ) was used for age and gender standardization. At diagnosis, both fasting and AUC C-peptide correlated with BMIZ (r=0.52, p<0.001 and r=0.34; p<0.001, respectively). C-peptide values were appreciably greater in the highest quartile of BMIZ than in the lowest quartile for both C-peptide measures (fasting C-peptide: 2.16±1.00 ng/ml vs. 0.91±0.56 ng/ml; p<0.001; AUC C-peptide: 488±201 ng/ml vs. 290±148 ng/ml; p<0.001). We also examined the association of the 30-0 minute C-peptide difference (early C-peptide response), previously shown to correlate with the first-phase insulin response, with BMIZ. There was little association between the early C-peptide response and BMIZ (r=0.08; p=0.44). The early C-peptide response values of the highest BMIZ quartile did not differ significantly from the lowest quartile values (1.60±1.31 ng/ml vs. 1.22±0.82 ng/ml, respectively; p=0.22). Among 84 children tested for HbA1c at diagnosis, HbA1c was significantly related to the early C-peptide response (r=0.32, p<0.01), but not to BMIZ (r=0.09, p=0.43). In conclusion, children with greater BMIZ values have higher fasting and AUC C-peptide levels at the diagnosis of T1D. The higher C-peptide levels appear to be indicative of greater insulin insensitivity rather than more remaining β-cell function, since the early C-peptide response is not related to BMIZ. Moreover, HbA1c and BMIZ are not related at diagnosis. If the fasting or AUC C-peptide are used to assess residual β-cell function at diagnosis, estimates could be inflated in children with more adiposity.

Supported By: National Institutes of Health

1300-P

MRI in Recent-Onset Type 1 Diabetes (T1D) Shows Reduced Pancreatic Volume and Altered Pancreatic Microstructure

JOHN M. VIROSTKO, CHRISTOPHER R. BOWMAN, JONATHAN M. WILLIAMS, WILLIAM E. RUSSELL, DANIEL J. MOORE, ALVIN C. POWERS, *Nashville, TN*

Recent studies have shown a reduced pancreas volume in adults with recent-onset T1D. Since islets account for only 1-2% of pancreatic mass, this suggests that pancreatic exocrine tissue is also altered in early T1D. These important initial studies did not include children, measured only total pancreatic volume, and did not perform longitudinal measurements in the same individual. To investigate pancreatic volume and microstructure shortly after the onset of T1D, we used a Philips 3 Tesla magnetic resonance imaging (MRI) scanner and advanced quantitative MRI techniques, including T2 relaxation mapping, apparent diffusion coefficient (ADC), and magnetization transfer ratio (MTR), to assess the pancreas in age-matched, healthy controls and individuals with recent-onset T1D (ages 8-35 yrs, avg. 13.2 ± 3.4). The same individual was scanned within 100 days of T1D diagnosis (Dx, avg. 55 d, range 31-98), at 6 months after Dx, and at 12 months after Dx. The MRI scan data from 13 T1D patients within 100 days of T1D Dx and 11 controls showed a trend towards a smaller pancreas volume index (PVI) (T1D vs. controls = 0.78 vs. 1.04, 25% decrease, p=0.08). In two individuals with T1D scanned at the three time points, the PVI was progressively smaller at 6 and 12 months after diagnosis, while a third individual with T1D displayed similar PVI longitudinally. The ADC, a marker for cell density, also showed a trend to being higher in T1D (1.45e-3 mm^2/s vs. 1.37e-3 mm^2/s, 6% increase, p=0.17), suggesting a decline in cell density. Neither the T2 relaxation time nor MTR was different in the T1D pancreas. These results suggest that children and adolescents with recent-onset T1D have reduced pancreatic volume and altered microstructure.

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1301-P

Predictors of Dyslipidemia over Time in Youth with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study

AMY S. SHAH, DAVID M. MAAHS, JEANETTE STAFFORD, LAWRENCE M. DOLAN, WEI LANG, GIUSEPPINA IMPERATORE, RONNY A. BELL, ANGELA D. LIESE, KRISTI REYNOLDS, CATHERINE PIHOKER, SANTICA MARCOVINA, DANA DABELEA, *Cincinnati, OH, Aurora, CO, Winston-Salem, NC, Atlanta, GA, Columbia, SC, Pasadena, CA, Seattle, WA*

Little is known about the evolution of dyslipidemia in youth with type 1 diabetes (T1D). Understanding risk factors for progression or regression of dyslipidemia may guide treatment.

We studied 1478 T1D youth not on lipid meds (50% male, 77% non-Hispanic white (NHW), baseline age 10.8±3.9 years) at baseline and follow-up (mean 7.1 years). Progression of dyslipidemia was defined as normal at baseline and abnormal at follow-up (abnormal defined as non-HDL-C>130 or HDL-C<35mg/dL). Regression was defined as abnormal at baseline and normal at follow-up. Multivariable logistic regression was used to examine predictors of progression and regression compared to stable normal and stable abnor-

mal, respectively. An area under the curve (AUC) variable was used for the time-varying covariates A1c and waist to height ratio (WHR).

Non-HDL-C progressed, regressed, was stable normal and stable abnormal in 19%, 5%, 69% and 7%, respectively. Corresponding percentages for HDL-C were 3%, 3%, 94% and 1%. Predictors of non-HDL-C progression were higher insulin dose at follow-up, A1c AUC, and WHR AUC (Table). Non-HDL-C regression was associated with NHW race-ethnicity and lower WHR AUC. HDL-C progression was associated with higher WHR AUC. HDL-C regression was not modeled due to small numbers.

A1c and WHR are modifiable risk factors of progressing dyslipidemia and may influence cardiovascular outcomes in youth with T1D.

Table.

	Non-HDL-C Progression		Non-HDL-C Regression		HDL-C Progression	
Significant covariates	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Race/ethnicity: other vs. NHW	1.22 (0.83, 1.77)	0.3089	**0.30 (0.10, 0.89)**	**0.0299**	0.97 (0.40, 2.33)	0.9433
Insulin dose per kg at follow-up (I unit increase)	**1.63 (1.13, 2.36)**	**0.0095**	0.85 (0.32, 2.28)	0.7477	0.86 (0.32, 2.27)	0.7542
A1c AUC (1 unit increase)	**1.39 (1.24, 1.56)**	**<.0001**	0.81 (0.61, 1.08)	0.1493	1.18 (0.91, 1.53)	0.2227
WHR AUC (0.1 unit increase)	**1.83 (1.43, 2.34)**	**<.0001**	**0.49 (0.28, 0.85)**	**0.0117**	**1.63 (1.02, 2.61)**	**0.0416**

Variables included in the above models: age and diabetes duration at initial visit, race/ethnicity, sex, current tobacco use and insulin dose/kg at follow-up, A1c AUC, and waist to height ratio AUC. Each model adjusted for clinical site, interval between baseline and follow-up, and season of follow-up visit. Only variables significant (p<0.05) for at least one outcome are listed.

Supported By: Centers for Disease Control and Prevention; National Institute of Diabetes and Digestive and Kidney Diseases

1302-P

Self-Monitored Blood Glucose Tests Performed Per Day Is an Important Marker of Racial Disparity in Behavior and HbA1c among Youth with Type 1 Diabetes

STUART CHALEW, RICARDO GOMEZ, ALFONSO VARGAS, CRUZ VELASCO-GONZALEZ, JODI KAMPS, RICHARD SCRIBNER, BRITTNEY JURGEN, JAMES HEMPE, *New Orleans, LA*

Attention to details of management plays an important role in achieving optimal diabetes outcome. The number of Self-Monitored Blood Glucose (SMBG) tests performed per day (TPPD) has been linked with HbA1c and mode of insulin delivery. Furthermore, TPPD has been reported to be less in black than in white youth. We hypothesized that psycho-social-economic factors are contributors to racial disparity in TPPD. SMBG data was collected during clinic visits from a biracial sample of youth (n=86) with T1D in New Orleans whose families self-identified as either black (n=33) or white (n=53). TPPD and mean blood glucose (MBG) from SMBG for the prior 30 days was obtained. In addition, HbA1c and information on family income, concentrated disadvantage (CDI), psychological depression level (DL), mother educational attainment (MEA), insulin delivery method (IDM) was also collected. Factors potentially influencing TPPD were analyzed using multiple variable linear modelling. In simple correlation TPPD was highly associated with HbA1c (r=-0.51, p<0.0001) and MBG (r=-0.28, p=0.009). In the statistical models race, age and IDM accounted for the largest amount of the variance in the model r^2=0.496. Addition of gender, income level, CDI, MEA, or DL and interactions to this model were not significant as covariates. TPPD declined with age, was less in blacks than whites across the spectrum of age and was higher in patients on pumps. TPPD is an easily monitored marker of behavior strongly associated with HbA1c. Racial disparity in TPPD may reflect behaviors and cultural differences that are not fully explained by income, CDI, depression or educational level. Identificiation of factors underlying racial disparity in TPPD may help in in designing better interventions to improve glycemic control in high risk populations.

Supported By: Mid-South Transdisciplinary Collaborative Center for Health Disparities Research

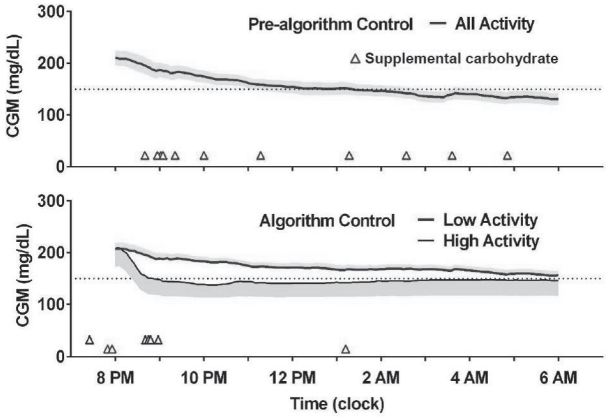
1303-P

Adjusting Insulin Delivery to Activity (AIDA) in Children with Type 1 Diabetes

PAULINA ORTIZ-RUBIO, ADEOLU OLADUNJOYE, MICHAEL AGUS, GARRY M. STEIL, *Boston, MA*

Physical activity in children with type 1 diabetes is associated with nocturnal hypoglycemia. We assess the feasibility of using daytime activity (DA) to adjust nighttime basal rates to prevent nocturnal hypoglycemia. Six children 7 to 17 years old with type 1 diabetes on insulin pump therapy have been enrolled. Each child wears a FitBit activity monitor and CGM for 3 months, with daily upload of data to HIPAA-protected, investigator-accessible cloud-based storage. An initial 2-week period is used to establish baseline DA and assess its effect on nighttime nadir (NN) glucose. Nighttime basal rates are adjusted following a multi-input-multi-output proportional integral (MIMO-PI) algorithm until nighttime target is achieved. Six subjects have been enrolled, and in all subjects DA was a significant predictor of NN. In the single subject who has completed the study to date, regression analysis indicated a significant relationship between DA and NN after 20 days (NN=-0.0081·DA+171 mg/dL; p=0.028). Prior to algorithmic control, the child's parents gave nighttime rescue 11 times (Figure, top). Following algorithmic nighttime basal adjustments, no hypoglycemic events occurred after 10 PM on 6 high activity days (Figure, bottom). Morning target (150 mg/dl) was achieved for both activity levels. We conclude basal rates can be adapted to monitored activity levels and that the process can be automated using MIMO-PI approach.

Figure.



Supported By: Legacy Heritage Fund

1304-P

Negative Impact of Higher Body Mass Index on Cardiac Autonomic Function in Adolescents with Type 1 Diabetes

YOON HI CHO, MARIA E. CRAIG, KIM C. DONAGHUE, *Westmead, Australia, Sydney, Australia*

We examined the longitudinal relationship between body mass index (BMI) and cardiac autonomic dysfunction in 253 adolescents (49% male) with type 1 diabetes (T1D). Heart rate variability (HRV) was assessed by 10-minute ECG recording using LabChart Pro: standard deviation of RR intervals (SDNN), root mean squared difference of successive RR intervals (RMSSD), triangular index (TI) and low frequency to high frequency ratio (LF:HF). At baseline, mean age was 14.3±2.7 yrs, T1D duration 7.1±3.7 yrs, HbA1c 8.3±1.5% (67±16mmol/mol), total daily insulin dose (TDD) 0.99±0.31U and BMI SDS 0.74±0.74. 33% of participants were overweight or obese. At follow up (3.0±0.7 yrs), mean HbA1c rose to 9.1±1.6% (76±18mmol/mol; p<0.001), while mean TDD and BMI SDS did not change significantly. Using generalised estimating equations (GEE), higher BMI SDS and HbA1c were significant predictors of lower overall HRV (SDNN, RMSSD and TI), whilst higher HbA1c, older age and male gender were significantly associated with higher LF:HF (indicating abnormal sympathetic/vagal balance, Table). Thus, higher BMI appears to contribute to adverse cardiac autonomic profile in T1D adolescents, independent of HbA1c. Interventions targeting overweight and obesity during adolescence may optimise long-term vascular health in T1D.

Table. Clinical Predictors of Heart Rate Variability Using Multivariable GEE.

HRV outcome	Predictor	B (95% CI)	*P*
SDNN	BMI SDS	-5.8 (-9.8 to -1.8)	0.004
	HbA1c	-4.4 (-5.9 to -2.8)	<0.001
RMSSD	BMI SDS	-6.6 (-12.3 to -0.8)	0.03
	HbA1c	-5.2 (-7.4 to -3.0)	<0.001
LF:HF ratio	Age	0.06 (0.02 to 0.09)	0.001
	HbA1c	0.1 (0.02 to 0.2)	0.01
	Female gender	-0.3 (-0.5 to -0.1)	0.001

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1305-P

Acute Kidney Injury in Childhood DKA Is Associated with Elevated Corrected Na, Hematocrit, and Heart Rate at Presentation

BRENDEN E. HURSH, REBECCA RONSLEY, CLAIRE RONSLEY, CHERRY MAMMEN, CONSTADINA PANAGIOTOPOULOS, *Vancouver, BC, Canada*

This study sought to determine the prevalence of acute kidney injury (AKI) in children ≤18 years with type 1 diabetes (T1D) presenting in diabetic ketoacidosis (DKA), and to assess for associated clinical markers of AKI. A retrospective review of all DKA admissions to BC Children's Hospital (09/2008 - 12/2013) was performed. The primary outcome measure, AKI, was defined using Kidney Disease/Improving Global Outcomes criteria. An estimated baseline glomerular filtration rate of 120 ml/min/1.73m^2 was used to calculate baseline serum creatinine using height and the bedside Schwartz equation. Of 194 eligible admissions, 46% were male with a mean age of 9.7 years (range 0.6-17.8); 72% had newly diagnosed T1D. AKI occurred in 64% of children with DKA; of these, 23.6% met criteria for stage 1 AKI, 30% for stage 2 AKI, and 10% for stage 3 AKI, with 2 requiring dialysis. A linear regression model assessed for clinical and biochemical markers associated with AKI. Using the ratio of initial creatinine to expected baseline creatinine as the dependent variable, the model explained 34% of the variance in creatinine elevation. Higher initial corrected Na had the strongest association with AKI (Beta 0.302; p<0.001). Also, higher initial hematocrit (Beta 0.262; p=0.004) and higher initial heart rate (Beta 0.240; p=0.004) were associated with the presence of AKI. Initial bicarbonate, age, sex, ICU admission and new diagnosis of T1D were not significant in this model. This study presents the first report of the high prevalence of AKI in children with DKA. The association with traditional markers of volume depletion reinforces the importance of accurate fluid status estimation and may help identify children who are likely to have associated AKI. As AKI carries a risk for chronic kidney disease, protocols for AKI identification and management need to be developed. Further prospective studies are required to better understand risk factors for AKI and long-term outcomes of AKI in childhood DKA.

1306-P

Labile Hemoglobin A1c (HbA1c) Is Higher in Blacks than Whites at the Same Glucose Level: A Precursor to Racial Disparity in Stable HbA1c

STUART CHALEW, JAMES HEMPE, *New Orleans, LA*

Higher stable hemoglobin A1c (S-A1c) levels have been observed in blacks compared to whites with similar mean blood glucose (MBG) (Diabetes Care 33:1025). The present study used capillary isoelectric focusing (CIEF) to quantify S-A1c and two labile hemoglobin complexes present in the CIEF A1c analytical fraction (Anal Biochem 424:149) in a biracial sample of youth with type 1 diabetes. S-A1c, labile A1c1, labile A1c2 and concurrent glucose were measured at clinic in 32 black (18F, 14M) and 52 white (22F, 30M) patients. MBG for the prior 30 days was calculated from patient glucose meters. Simple differences between group means were assessed by t-test. The influence of race was further assessed in multiple variable regression models, with group differences tested on adjusted LS means. The results showed that blacks had higher S-A1c levels than whites (p=0.0363) even after adjustment for MBG (p<0.0001), chronologic age (p=0.0086) and gender (p=NS) (overall model r^2=0.58, p<0.0001). Total labile A1c (L-A1c=labile A1c1+labile A1c2) was positively correlated with concurrent blood glucose. L-A1c remained higher in blacks (LSMean=4.8) compared to whites (LSMean=4.1) even after adjustment for concurrent glucose and chronologic age (overall model r^2=0.44, p<0.0001). Labile A1c1, but not labile A1c2, was higher in blacks than whites when adjusted for concurrent glucose. We conclude that MBG-independent racial disparity is evident in both stable and labile components of the CIEF A1c analytical fraction. The chemical identities of these labile hemoglobin complexes are currently unknown. Further study of the biochemistry of these complexes and factors that influence their synthesis or decomposition could help explain the mechanism of MBG-independent racial disparity in S-A1c. And also improve how glycated hemoglobin information is used to diagnose diabetes and assess glycemic control in mixed race populations.

Supported By: Mid-South Transdisciplinary Collaborative Center for Health Disparities Research

1307-P

Association of Parental Acculturation and Type 1 Diabetes in Hispanic Youth: A Pilot Study

KAJAL GANDHI, BARBARA J. ANDERSON, NIDHI BANSAL, MARIA J. REDONDO, TOM BARANOWSKI, *Houston, TX*

50% of Hispanic-American youth with type 1 diabetes (T1D) are in suboptimal glycemic control, and understanding the factors contributing to this high risk status is critical. Acculturation, a process by which an ethnic group adopts the cultural patterns of a host population, has been associated with both improved and worsened health outcomes. "Bicultural" subjects identify themselves as part of both their native and host cultures, usually determined by self-report; previous studies suggest this may be more ideal for pediatric health outcomes.

This pilot, cross sectional study investigated the associations among parental acculturation and diabetes related care/outcomes among Hispanic-American youth with T1D, 2-14 years old at Texas Children's Hospital. Bi-Dimensional Acculturation Scale for Hispanics, Nutrition Knowledge Survey (NKS), Diabetes Self-Management Questionnaire, and Trust in Physician Scale were administered. Demographic/clinical information was obtained by chart review.

Among Hispanics (n=31), children of "Bicultural" parents had significantly lower hemoglobin A1c (mean 7.8%) than those with "non-Hispanic" (mean 9.2%) (p<0.05) and "Hispanic" (mean 9%) acculturation status, after controlling for insurance status and type of insulin therapy. "Bicultural" parents had higher nutrition knowledge scores than "Hispanic" parents, but this effect was not significant between groups (p =0.31). Physician trust was high. "Bi-Cultural" parents were also more likely than "non-Hispanic" parents to have children who followed the T1D nutrition plan and were less likely to miss insulin doses.

Hispanic parents with "Bi-Cultural" orientation had youth in better glycemic control and T1D management as compared to "non-Hispanic" and "Hispanic" oriented parents. More culturally sensitive diabetes education and care may decrease disparities in health outcomes among diverse T1D youth.

1308-P

The Association of Clinic Driving Distance on Glucose Control and Management of Children with Type 1 Diabetes

RANSOME EKE, JOEL E. WILLIAMS, PATRICIA CARBAJALES-DALE, CHRYSTAL SCHAUDER, LISA LOOPER, CARRIE FROST, BRYCE A. NELSON, *Clemson, SC, Greenville, SC*

The management of children with type 1 diabetes (T1D) has improved over the years with advent use of multiple daily injection regimens, insulin pump therapy and continuous glucose monitoring, yet achieving recommended glycated hemoglobin (HbA1c) levels is still a major concern. It is currently unknown if distance to endocrinology specialists may negatively affect the utilization of their services and HbA1c control. We retrospectively analyzed distance and driving time to our 3 endocrinology office locations and its impact on HbA1c levels among 477 pediatric patients with T1D during June 2014-May 2015. Repeated measurements of HbA1c were extracted, and distance and driving time to care facility were estimated using SAS and Google Maps. We examined the association between distances and mean HbA1c levels and estimated the adjusted risk ratio (RR) using generalized linear model procedure, applying Poisson regression with robust error variance. The median age, duration of illness and driving distance were 13 years, 3 years and 17 miles, respectively. The mean HbA1c ranged from 5% to 15%. Results of the generalized linear model showed that children who receive specialist care within 20 miles distance from their home have better glucose control than those beyond 20 miles distance to care facility (RR, 0.96; 95% C.I., 0.93-0.99; p-value, 0.01). Comparing effect of race on HbA1c control within 20 miles distance, whites had better control than blacks (RR, 0.89; 95% C.I., 0.84-0.95). However, no racial difference was seen beyond 20 miles. Our study suggests that increased driving distance to endocrinology clinics is significantly associated with poor HbA1c control in children with T1D. Integrating mobile health technology into care of patients with T1D may bridge the gap in driving distance and help improve glucose control in this population.

1309-P

Relationship of Serum Proinsulin Relative to C-Peptide Secretion in Subjects with Long-Standing Type 1 Diabetes

EMILY K. SIMS, LINDA A. DIMEGLIO, ANTHONY J. ACTON, RAGHAVENDRA G. MIRMIRA, CARMELLA EVANS-MOLINA, *Indianapolis, IN*

We previously demonstrated increased circulating total proinsulin (PI) relative to C-peptide (PI:C ratios) in persons newly diagnosed with type 1 diabetes (T1D) compared to healthy controls, suggesting β-cell ER dysfunction and stress. We also demonstrated that PI rose as C-peptide increased during the honeymoon period. However, it remains unknown how β-cell proinsulin release in longstanding T1D correlates with C-peptide secretion. To define this, we assayed fasting sera banked from 40 subjects enrolled in the T1D Exchange clinic registry (age: 37 ±18 years, T1D duration: 18 ±16 years, A1c:

7.9% ±1.7), determined to be either C-peptide negative or positive based on mixed-meal tolerance testing (n=20/group). Intact and total proinsulin levels were measured using Stellex chemiluminescent assays (ALPCO). C-peptide values were measured using a TOSOH immunoassay. PI:C ratios were calculated as molar ratios; values were multiplied by 100 to obtain intact proinsulin as a % of C-peptide. Spearman correlations were used to assess relationships between variables. Two C-peptide negative subjects (10%) had detectable PI. In C-peptide positive subjects, fasting intact PI:C ratios demonstrated a negative correlation with stimulated C-peptide values (r=-0.503, p=0.028) and a positive correlation with hemoglobin A1c (r=0.62, p=0.003). No significant correlations with age, age at diagnosis, T1D duration, or body mass index were detected. Lastly, intact and total proinsulin values were highly correlated (r=0.88, p<0.001). Our results suggest continued β-cell ER dysfunction in C-peptide positive, as well as a subset of C-peptide negative subjects with T1D. The strong correlation between intact and total proinsulin values suggests that either assay could provide useful information in this population. Future work is needed with longitudinal samples and larger sample sizes to increase the power to detect significant relationships with other key subject characteristics.

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1310-P

Barriers in Pediatric Diabetes Device Downloads

SANIYA KISHNANI, JESSICA DROBNY, NICOLE SCHLEIFER, BARRY CONRAD, TANDY AYE, *Palo Alto, CA*

Technology has an increasingly important role in the treatment of children with type 1 diabetes (T1D). The use of blood glucose meters (BGMs), insulin pumps, and continuous glucose monitors (CGMs) are becoming new standards of care. During clinic visits, providers and certified diabetes educators (CDEs) teach children and families how to download these devices and review patterns. In this cross-sectional study, we sought to see which patient characteristics predict for a higher likelihood of downloading diabetes devices in the home setting. All patients and/or parent (s) seen at the Stanford Children's Diabetes Clinics during a consecutive 100 day period completed a survey. The patients' diabetes history and device downloading practices were asked and this data was entered into REDCap database. A chi-square test of independence was used to analyze the likelihood of downloading based on device type, age, duration of diabetes and hemoglobin A1c (HgbA1c). 359/366 families completed the survey. Analysis showed 41.5%, 36.0%, and 18.6% of participants, downloaded their BGM, insulin pumps, and CGMs, respectively. Parents of children ages 0-6 years were more likely to download (p=0.004). The duration of T1D did not influence downloading practices. Those who downloaded had better control (HgbA1c < 8.5%, p=0.048). Multiple categories of barriers (resources, technology and education) to downloading were reported. However, despite this, 38.6% of the patients who reported these barriers, still downloaded their devices to look for patterns and manage their diabetes between visits. Downloading data from diabetes devices can help patients with T1D use the data more effectively and improve glycemic control. Further research in educational and motivational interventions in identifying barriers and improving ease of access in downloading will improve the level of care in T1D.

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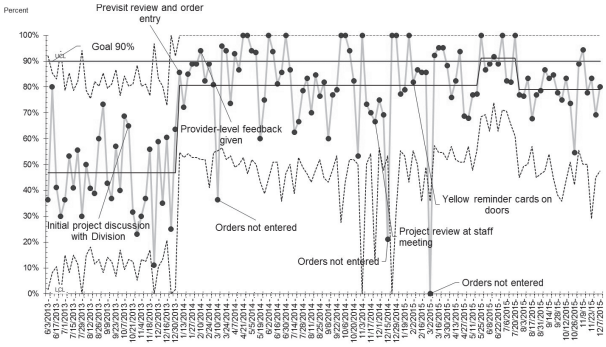
1311-P

Improving Urine Microalbumin Screening in a Pediatric Diabetes Clinic

KARISHMA DATYE, BARRON PATTERSON, *Nashville, TN*

Diabetic nephropathy, a serious complication of diabetes, can be detected early with urine microalbumin testing which can allow for timely intervention. Our goal was to increase annual urine microalbumin screening in patients with type 1 and type 2 diabetes to over 90% (up from 49%) at a busy urban center that serves over 2700 pediatric diabetes patients annually (over 85% of patients diagnosed with type 1 diabetes). A multidisciplinary group utilized the 2014 American Diabetes Association microalbumin screening recommendations and identified patients in need of screening prior to clinic visits. Serial Plan-Do-Study-Act (PDSA) cycles were used to ensure that eligible patients had urine microalbumin orders prior to their visit and that urine specimens were actually obtained. Weekly screening results were plotted using a P chart (Figure 1) to determine when improvement was achieved. Interventions began January 2014. An immediate effect was seen, and sustained non-random improvement was achieved. Our weekly screening rates went from a baseline of 46.8% to 79-91%. By the end of 2015, cumulatively 93% of eligible patients had received their annual screening microalbumin test. These data show sustained improvement in urine microalbumin annual screening in a large pediatric diabetes practice. Next steps are to determine whether increased screening led to improved detection and treatment of renal disease in our patients.

Figure 1. Percent of Eligible Patients with Diabetes Screened for Urine Microalbumin in Eskind Diabetes Clinic by Week (P-Chart).



1312-P

Hyper-IgA at Onset of Type 1 Diabetes

MARIA J. REDONDO, DAVID GOMEZ, NICHOLAS RIDER, SRIDEVI DEVARAJ, MASSIMO PIETROPAOLO, KATHERINE HWU, *Houston, TX*

Hyperproduction of IgA has been sporadically reported in autoimmune diseases including type 1 diabetes (T1D) and hypothesized to result from toll-like receptor (TLR) activation of β-cells, originate from gut mucosa and contribute to microangiopathy in type 2 diabetes. We studied serum IgA and clinical parameters in children with new onset T1D.

We analyzed a cross-sectional series of 707 children 9.7 [4.4] (mean [SD)] years old (58.6% non-Hispanic white, 21.1% Hispanic, 15.4% black, 4.9% other) with new onset T1D diagnosed between 1/2008-2/2012. A subset of 82 children 10.6 [4.2] years old diagnosed between 11/2010-10/2011 was followed for up to 4.8 years. Demographic and clinical variables were analyzed. IgA values below and above age-adjusted normal ranges were defined as IgA deficiency or hyper-IgA, respectively.

At the onset of T1D, hyper-IgA occurred in 19.9% (141/707) of the children. By multivariable analysis, compared with children with normal IgA, those with hyper-IgA were more likely to be Hispanic and had higher hemoglobin A1c (A1c) and glucose (p<0.0001). Higher IgA levels were significantly associated with age, Hispanic ethnicity, A1c, diabetic ketoacidosis (DKA) and T1D onset in cold months (September to February) (p<0.0001, r2=0.18). Exclusion of children with IgA deficiency did not change the results (p<0.0001, r2=0.20).

In the prospective cohort, 60% (9/15) of the children with hyper-IgA at onset still had hyper-IgA 1.9 [1.15] years later, and 4 children consistently had hyper-IgA on 4 interval measurements during 3.7 [0.68] years. Hyper-IgA at onset or persistently thereafter were not associated with A1c levels or presence of microalbuminuria on follow-up.

In conclusion, about 20% of children with new onset T1D have hyper-IgA that can persist for years. Age, A1c and DKA at onset, Hispanic ethnicity and season of T1D onset are independently associated with IgA levels at onset. Further studies are warranted to investigate the role of infection, subsequent TLR activation of β-cells and IgA responses.

Supported By: Texas Children's Hospital

1313-P

Glycemic Control Is Unchanged in Youth with Type 1 Diabetes Using Telemedicine for Clinical Care

R. PAUL WADWA, NHUNG NGUYEN, COLLEEN L. WOOD, CIERRA SULLIVAN, JOHN F. THOMAS, *Aurora, CO, Billings, MT*

Youth with type 1 diabetes (T1D) living in rural areas often have limited access to pediatric endocrinologists, which may impact their ability to obtain optimal glycemic control. Our clinic has provided T1D clinical care via telemedicine since 2012. The telemedicine clinics include pediatric endocrinologists in Aurora, Colorado videoconferencing with patients at hospital-based diabetes centers in Casper and Cheyenne, Wyoming. In this study, we analyzed data from 21 pediatric T1D patients with at least 2 years (≥ 22 months) of follow up after initial use of telemedicine for T1D care. Patients seen at telemedicine sites in Casper (38%) and Cheyenne (62%), were 76% male, had mean age 11.5 ± 3.9 years and T1D duration 5.0 ± 3.8 years at the initial tele-

For author disclosure information, see page A696.

medicine visit. Of the 21 subjects, 86% had private insurance and 48% were on insulin pumps. Mean hemoglobin A1c (A1c) did not significantly change from initial telemedicine visit (A1c 9.2 ± 1.6%) to the 2 year follow up visit (A1c 9.4 ± 1.8%, p=0.60) but visit frequency was significantly increased with telemedicine compared to the year prior to using telemedicine (2.1 ± 1.2 prior vs. 2.9 ± 1.2 visits/year with telemedicine, p=0.01). Glycemic control varied greatly in this cohort (A1c range 7.1-13.7% at 2-year follow up) with almost half of the group (48%) having lower A1c values at follow up compared to A1c at the initial telemedicine visit. Most patients (95%) did not achieve ADA recommended A1c targets (A1c< 7.5%). Change in A1c over the 2-year time period was not significantly associated with age, T1D duration, insurance status, insulin pump use, visit frequency or baseline A1c (p>0.05 for all correlation coefficients). In summary, telemedicine provides increased access to subspecialist diabetes care for pediatric T1D patients while maintaining glycemic control. Further evaluation is needed to determine the effects of telemedicine on long term glycemic control and risk for diabetes complications in T1D patients.

1314-P

Differential Clinical Phenotypes between Adult-Onset and Childhood-Onset Type 1 Diabetes Mellitus (T1DM) in a Chinese Population

WENQIAN REN, HAIXIA XU, JINHUA YAN, DAIZHI YANG, SIHUI LUO, XUEYING ZHENG, LILING QIU, BIN YAO, JIANPING WENG, *Guangzhou, China*

Differential clinical characteristics between childhood-onset and adult-onset T1DM have been explored in Caucasians. However, little is known about those in Chinese patients, partially due to its low incidence in China. By using the latest T1DM Registry Study in Chinese population, Guangdong type 1 diabetes Translational Study, clinical phenotypes between childhood-onset and adult-onset T1DM were compared. 716 T1DM patients registered between 2011 and 2015 with disease duration no more than 5 years were selected. Among them, 258 patients with an age of onset below 18 years were assigned into childhood-onset group (CG) while the rest 458 constituted the adult-onset group (AG). Disease onset was more rapid and symptomatic in CG than AG, which is reflected by shorter symptomatic period pre-diagnosis, higher prevalence of diabetic ketoacidosis comorbidity (P<0.001). In addition, any combinations of positive autoimmune antibodies (GAD, ICA512, ZnT8) were more frequently observed in CG than those of AG (P<0.001). In accordance with the clinical manifestation, patients in CG showed more severely impaired endogenous islet β-cell function, which was evidenced by statistically lower serum level of both fasting and 2 hour postprandial C peptide (PCP2h) than AG. Moreover, average insulin dosage was higher in patients of CG (P<0.001), which instead leading to increased HbA1c than those of AG. Further analysis of HbA1c associated risk factors revealed that high average insulin dosage and conventional regimen of one or two insulin injections per day in CG strongly related to inadequate glycemic control, while uncontrolled diet, smoking, household income and low PCP2h level in AG. In conclusion, Chinese type 1 diabetic patients exhibited significant differences in clinical phenotypes and risk factors for glycemic control, which may indicate different interventional strategy.

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1315-P

Modifiable and Nonmodifiable Predictors of Acute Complications in Teens with Type 1 Diabetes (T1D)

LISA K. VOLKENING, WENDY L. LEVY, JESSICA L. ELBACH, ANITA L. KAO, YULIANA ROJAS, CAROLINE J. GONYNOR, BARBARA J. ANDERSON, LORI M. LAFFEL, *Boston, MA, Houston, TX*

Acute complications contribute to substantial morbidity and healthcare costs in youth with T1D. Adolescence is a critical period of deteriorating glycemic control, placing teens at high risk for acute complications. To evaluate incidence rates (IRs) and predictors of acute complications in this vulnerable age group, we captured diabetes-related emergency room (ER) visits, hospitalizations, and episodes of severe hypoglycemia (hypo) in 307 teens (50% male, 79% white) with T1D of >1 yr duration from 2 large pediatric diabetes centers in the U.S. Mean age was 15.0±1.3 yrs; T1D duration was 6.6±3.7 yrs; A1c was 8.5±1.1%; 64% were insulin pump treated; and 29% used CGM at some time during the observation period. Acute events were captured by patient/family interview at quarterly visits and confirmed in the medical record. IRs were calculated per 100 patient-years (100 pt-yrs). Each teen contributed a mean of 1.3±0.4 yrs of follow-up data. Over a total of 404.9 pt-yrs, there were 39 diabetes-related ER visits (IR=9.6/100 pt-yrs), 14 diabetes-related hospitalizations (IR=3.5/100 pt-yrs), 154 episodes of severe hypo requiring assistance with oral treatment (IR=38.0/100 pt-yrs), and 33 episodes of severe hypo resulting in seizure, loss of consciousness, or requiring glucagon or IV dextrose (IR=8.2/100 pt-yrs). In bivariate analyses, non-white race and baseline A1c ≥9.0% were associated with higher IR of ER visits; injection regimen, no CGM use during follow-up, and baseline A1c ≥9.0% were associated with higher IR of hospitalization; and younger age, non-white race, CGM use at some point during follow-up, and baseline A1c <8.0% were associated with higher IR of severe hypo (all p≤.01). Race and age are non-modifiable predictors of ER visits and severe hypoglycemia; treatment variables (injections, CGM) and glycemic control are potentially modifiable factors associated with acute complications. Treatment factors may be markers of risk rather than mediators; future research is needed.

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1316-P

The Relationship between Patient-Driven Input and Glycemic Control in Youth with Type 1 Diabetes Mellitus in the STAR 3 Study

NICHOLAS A. DAVIS, DAVID H. JELLEY, *Tulsa, OK*

Previous studies have employed a variety of measures to characterize the glycemic variability in patients with type 1 diabetes mellitus (T1DM), using both sparse self-monitoring blood glucose (SMBG) and continuous glucose monitoring (CGM) data. The Sensor Augmented Pump Therapy for A1c Reduction Study (STAR 3) provides a wealth of CGM time series data on T1DM pediatric and adolescent patients, generated from sensor augmented pump therapy (SAPT) devices. The STAR3 study collaborators at Medtronic provided data on n=70 (39 males, 31 females) pediatric (52.9% ages 7-12) and adolescent (47.1% ages 13-18) patients, with a mean range of 490±130 days of CGM data, taken at 5-minute intervals. After daily aggregation there are ~25K records. Using daily variability measures over the entire measurement duration, we analyze the effect of patient-driven input on glycemic control. Patient-driven input parameters include: number of food-based, blood glucose-based, and manual insulin boluses per day, respectively; % of bolus insulin from food, blood glucose, and manual, respectively; % of total daily insulin dose from basal insulin (%TDD); grams carbohydrate entered per day. Additional parameters include patient age and sex. Outcome measures include HbA1c, weight, and BMI, each taken every 3 months during CGM duration; time < 60 mg/dL, < 70, in range 70-180, > 180, > 250, respectively; low and high blood glucose index (LBGI, HBGI), respectively; and daily relative risk (DRR). Linear regression was performed, as well as Spearman's rank correlation; $p < 0.05$ was considered significant. % bolus from food (Spearman .402) and %TDD (.156) were both positively correlated with time in range 70-180 mg/dL, while % of bolus from blood glucose negatively correlated. %TDD and % bolus from food were negatively correlated with HBGI and DRR. The results suggest that patient-driven food-based bolus insulin and basal rate (comprising %TDD) are critical factors in maintaining glycemic control.

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1317-P

Difficulties and Strategies for Patients with Autism Spectrum Disorder and Type 1 Diabetes

KELLY STANEK, JENNIFER K. RAYMOND, SHIDEH MAJIDI, *La Mirada, CA, Aurora, CO*

In current Autism Spectrum Disorder (ASD) and type 1 diabetes (T1D) literature, there are no studies addressing the management and care of people with both disorders. Though the population with both diagnoses is small, the challenges and management strategies are unique and warrant evaluation. Through retrospective chart review, patients (n=30) with both T1D and ASD were identified. Parents were contacted by phone and invited to complete a questionnaire focusing on the difficulties in diabetes management in children with ASD and strategies they have found useful. Ten families consented to complete the questionnaire. ASD included diagnoses of Autism (3; 30%), Asperger's Syndrome (4; 40%), and Pervasive Developmental Disorder (1; 10%). Two families did not provide specific diagnoses within ASD. The disease status was noted as mild in 5 patients and moderate in 5 patients. The patients were an average of 12.6 years (range 8-18 years). Half reported using an insulin pump and half use a continuous glucose monitor (CGM). Changes in dietary habits (80%), followed by carbohydrate counting (60%) were considered the most difficult part of management. Only 1 (10%) child can independently draw up insulin, while 6 (60%) can check blood glucose independently. Half of the families had no strategy to help with difficulties in diabetes. Others used switching to insulin pump therapy (3; 30%) and picture/visual schedule or aid (2; 20%). In the ASD and T1D population,

carbohydrate counting, changes in dietary habits, and drawing insulin independently may pose the biggest challenges. Half do not have a strategy to address difficulties in diabetes management; indicating increasing knowledge of available tools and strategies might be helpful in improving care in this population. Families report switching to an insulin pump, using a CGM, and visual aids can help with diabetes management. Further studies in larger patient populations are needed to help determine how to provide optimal care to this group.

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1318-P

Caring for a Child with Diabetes in a Food-Insecure Household: A Qualitative Study

NASEEM Y. ALYAHYAWI, CATHERINE COX, AMY Y. ORNSTEIN, ELIZABETH CUMMINGS, *Jeddah, Saudi Arabia, Halifax, NS, Canada*

A recent Canadian study found a high rate (21%) of food insecurity (FI) in families with a child with diabetes (DM), however, little is known about the impact of FI on families. Our qualitative study aimed to describe the experience of families with children with insulin requiring DM living with FI.

Caregivers of children with insulin requiring DM self-identified through our tertiary care diabetes clinic. Food security status was verified via standardized FI questionnaire used in the Canadian Community Health Survey. Semi-structured telephone interviews were conducted centred around caregivers' experiences, coping and perceptions of social supports to gain in depth understanding of their lived experience. Thematic analysis was performed by 2 researchers independently from interview transcripts using Nvivo software. Owen's criteria were used to synthesize major themes.

Caregivers described a complex relationship between FI and DM. Major themes identified include: 1.) Caring for a child with insulin requiring DM aggravates FI and exacerbates financial and emotional strain. DM contributes to FI in many ways including higher cost of healthy and portable food (hypoglycemia kit) and diabetes supplies. 2.) Caregivers in FI households employ many coping strategies to mitigate the impact of FI and meet the child's diabetes needs. For example they describe spending significant time and effort on strategic grocery shopping. 3.) Caregivers perceived difficulty accessing supports, such as school breakfast programs and food banks, due to concerns of lack of fit with the child's DM needs.

Caring for a child with insulin requiring DM in a food insecure household poses unique challenges that contribute to FI and diabetes-related distress. Food insecure families struggle to meet common diabetes dietary and hypoglycemia recommendations and report barriers to using traditional supports for FI families. This study highlights the need for diabetes clinicians to identify FI and advocate for improved family supports.

1319-P

A Longitudinal Investigation of Cognitive Function in Youth with Type 1 Diabetes Mellitus

BRENDA A. KIRCHHOFF, DUSTIN K. JUNDT, TASHA DOTY, TAMARA HERSHEY, *St. Louis, MO*

Although cross-sectional studies find altered cognition in youth with type 1 diabetes, few longitudinal studies have examined the trajectories of their cognitive development over time. To determine whether cognitive differences between youth with type 1 diabetes and controls are maintained, increase, or decrease across time, and if glycemic control and age of onset influence the trajectories of cognitive function in diabetic youth, we assessed intelligence, delayed memory, and processing speed at three time points in youth with type 1 diabetes and sibling controls (aged 4-16). Hierarchical linear modeling was used to examine the relationships between diabetes, hyperglycemia (HbA1c values), age of onset, and cognition over 5.5 years. Youth with diabetes performed worse than controls on visual-spatial intelligence and visual-spatial delayed memory tasks over time, and did not improve as much in processing speed as controls. Higher mean HbA1c values were associated with lower verbal intelligence and slower processing speed but better delayed verbal memory across all time points. Higher mean HbA1c levels had a more pronounced negative effect on visual-spatial intelligence for youth with early onset than later onset diabetes. Importantly, within-person decreases in HbA1c values were associated with improved visual-spatial intelligence task performance and faster processing speed. Thus, the results of this study demonstrate that hyperglycemia and age of onset can alter the developmental trajectories of cognitive processes in youth with type 1 diabetes. They also suggest that treatments that lower hyperglycemia could lead to improvements in cognitive function in youth with type 1 diabetes over relatively short time periods.

Supported By: National Institutes of Health; Dana Foundation

1320-P

WITHDRAWN

1321-P

High Incidence of Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes among Polish Children Aged 10-12 and up to 5 Years of Age: A Multicenter Study

AGNIESZKA SZYPOWSKA, KATARZYNA DZYGAŁO, MARTA WYSOCKA-MINCEWICZ, ARTUR MAZUR, LUCYNA LISOWICZ, IWONA BEN-SKOWRONEK, JOANNA SIENIAWSKA, BOŻENA KŁONOWSKA, DOROTA CHAREMSKA, JOLANTA NAWROTEK, IRENA JAŁOWIEC, ARTUR BOSSOWSKI, MILENA JAMIOŁKOWSKA, BEATA PYRZAK, IZABELA ROGOZIŃSKA, MIECZYSŁAW SZALECKI, *Warsaw, Poland, Rzeszów, Poland, Lublin, Poland, Olsztyn, Poland, Kielce, Poland, Białystok, Poland*

Objective: Despite its characteristic symptoms diabetes is still diagnosed late causing the development of diabetic ketoacidosis (DKA). The aim of this cohort study was to estimate the incidence of DKA and factors associated with the development of acidosis at diabetes recognition in Polish children aged 0-17.

Study Design: The study population consisted of 2100 children with newly diagnosed T1D in the years 2010-2014 in 7 hospitals in eastern and central Poland. The population living in these areas accounts for 35% of the Polish population. DKA was defined as a capillary pH <7.3. The analysed data included age, sex, diabetes recognition, pH, HbA1c, fasting C-peptide, BMI-SDS.

Results: DKA was observed in 28.6% of children. There were two peaks in DKA occurrence: in children <5 years of age (33.9%) and aged 10-12 (34%). The highest incidence of DKA was noted in children aged 0-2 (48.4%). In the group with DKA, moderate and severe DKA occurred in 46.7% of children. Girls and children <2 years of age were more prone to severe DKA. The multiple logistic regression analysis showed the following factors associated with DKA: age (p=0.002), fasting C-peptide (p=0.0001), HbA1c (p=0.0001), no family history of T1D (p=0.0001) and BMI-SDS (p=0.0001).

Conclusion: The incidence of DKA is high and remained unchanged over the last 5 years. Increasing the awareness of symptoms of DKA is recommended among children <5 years of age (especially <2 years of age) and aged 10-12. Children <2 years of age and girls were at the highest risk of severe DKA.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1322-P

Is Compliance with Diabetes Retinopathy (DR) Screening Associated with Achievement of Therapeutic Goals in Youth with Type 1 Diabetes (T1DM)?

PEDRO A. PAGÁN BANCHS, LAWRENCE J. SWANSON, ERIKA MCCANN, VINCENT C. ARENA, TINA COSTACOU, KANWAL NISCHAL, INGRID LIBMAN DE GORDON, *Pittsburgh, PA*

Despite advances in diabetes management in the past two decades, modern cohort data have shown that a significant number of youth with T1DM fail to meet therapeutic goals. DR screening is recommended by the ADA and ISPAD for children ≥ 10 years with T1DM duration ≥ 2 years. We hypothesized that compliance with DR screening would be associated with achievement of therapeutic targets as per the 2016 ADA Standard of Care (HgbA1c <7.5%, LDL <100 mg/dL).

As part of an ongoing study, medical records of 238 patients with T1DM (58% male, 88% Caucasian, mean age at DR screening: 15.3±2.9 years, mean duration of T1DM: 7.1±3.6 years), who underwent DR screening between 2/15 - 11/15 were reviewed. Information collected included DR status, anthropometric and laboratory characteristics at time of DR screening (for those screened in conjunction with their diabetes clinic visit, n=161) or at the time closer to their ophthalmology visit (for those screened at an outside institution, n=77).

Of these, 29.4% had a HgbA1c <7.5% (32% Caucasian vs. 7.7% African American, p=0.04) and 65.7% had an LDL-cholesterol <100 mg/dl (60% on multiple daily insulin injections vs. 73.4%, on continuous subcutaneous insulin infusion, p=0.04). Furthermore, 62% of the cohort had a body mass index <85% for age/gender (71% males vs. 40.5% females, p=0.001). There were no differences in achieving any of the therapeutic targets in those with evidence of retinopathy (n=8) vs. those without (n=230).

A significant proportion of children with T1DM, who comply with diabetes retinopathy screening, do not achieve the ADA therapeutic goals, regardless of DR status. Further studies are needed to confirm these findings.

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1323-P

Improving Data Quality in a Growing Pediatric Diabetes Registry from 2010 to 2015: The SWEET Initiative with 42 Centres from Five Continents

MICHAEL WITSCH, ANKE SCHWANDT, HENK J. VEEZE, STÉPHANE BESANÇON, BANSHI SABOO, MAURO SCHARF, DANIÈLE PACAUD, SWEET GROUP, *Luxembourg, Luxembourg, Ulm, Germany, Rotterdam, Netherlands, Bamako, Mali, Gujarat, India, Curitiba, Brazil, Calgary, AB, Canada*

"SWEET ("Better control in Pediatric and Adolescent diabeteS Working to CrEat CEnTers of Reference (CoR)") is a registered charity with close ties to the ISPAD. Since 2006 it aims to create and certify CoR for childhood diabetes in each country or region. One of the requirements is a continuous electronic documentation of at least 150 pediatric diabetes patients treated by a multidisciplinary team based on the ISPAD Clinical Practice recommendations. Currently, SWEET centers are present in 25 European countries, Canada, Costa Rica, Brazil and Mali. Smaller centers and centers that cannot comply with all requirements as yet, can participate as collaborative ones.

The SWEET dataset consists of a consented list of quality indicators reflecting high-level routine pediatric care, incorporating structural aspects as well as process and outcome of diabetes care. Anonymized data can be submitted by Excel files compliant with a standardized format or by use of a dedicated electronic health record (DPV software), currently available in English, French and German. These data are used for biannual benchmarking and for scientific analyses. Currently, 42 centers contributed longitudinal data of 22,427 patients (12,858 in 2015, median age 14.1 y, diabetes duration 4.8 y, TD1 95.8% TD2 1%, others 3.2%). Data completeness is improving from year to year (2010: HbA1c in 80.2%, BMI in 62.8%, 2014: 94.4% and 91.3%, respectively). Median HbA1c is 7.6%. 11 centers achieve a median HbA1c under 7.5%. As second quality instrument serve external peer audits at the CoR, based on NHS standard, with peer diabetologists and neutral experts jointly visiting the diabetes service. Biannual meetings (in person and web-based) of all SWEET members provide a forum to openly discuss results of benchmarking and audits, case reports, personal exchange and information on new developments. The SWEET group encourages sabbaticals and visits among the participating centers.

PREGNANCY—BASIC SCIENCE/TRANSLATIONAL

Moderated Poster Discussion: Unearthing the Molecular Mechanisms of Metabolic Disease in Mom and Baby *(Posters: 1324-P to 1331-P), see page 18.*

1324-P

DNA Hypermethylation Corresponds to Differences in Metabolism and Cellular Differentiation in Mesenchymal Stem Cells from Infants Born to Obese Mothers: The Healthy Start BabyBUMP Project

KRISTEN E. BOYLE, ZACHARY W. PATINKIN, ALLISON L.B. SHAPIRO, LAUREN VANDERLINDEN, KATERINA KECHRIS, DANA DABELEA, JACOB E. (JED) FRIEDMAN, *Aurora, CO*

Maternal obesity increases offspring risk for metabolic disease in later life, though the molecular mechanisms in humans are unclear. We have reported that mesenchymal stem cells derived from umbilical cord of infants born to obese (Ob-MSC) vs. normal weight mothers (NW-MSC) exhibit greater capacity for adipogenesis, but no difference in myogenesis, and have linked these differences to disruption of β-catenin signaling in Ob-MSC. Here, we tested the hypothesis that metabolic function would be compromised in myogenic differentiating Ob-MSC. MSCs were cultured from term infants born to obese (n=14; pre-pregnancy (pp) BMI = 34.6 ± 1.0 kg/m^2) or NW (n=15; (pp) BMI = 21.1 ± 0.3 kg/m^2) mothers. Cellular fatty acid oxidation (FAO) and insulin stimulated glucose uptake (ISGU) were measured at d21 of myogenesis. FAO was 30% lower (P<0.01) in Ob- vs. NW-MSC, while total AMPK was 25% lower (P<0.05) and phospho AMPK tended to be lower in Ob-MSC (-30%, P=0.09). There were no differences in ISGU. In undifferentiated MSC, targeted geneset analyses for significant differentially methylated DNA regions (Illumina 450K) underlying cellular differentiation or metabolic pathways revealed Ob-MSC hypermethylation for 8 genes in differentiation (including NOTCH4, CYP8B1), 3 genes in oxidative metabolism (PRKAG2, ACACB, CPT1A), and 5 genes in insulin signaling (PRKCZ, GCK, TNF, ADIPOQ, CACNA1D) pathways. β-value differences reflect 3-8%, 5-8%, and 3-7% higher DNA methylation in Ob-MSC for genes in these pathways, respectively (minimum P<0.005). Importantly, the differentiation pathway genes are linked to β-catenin signaling, while the oxidative metabolism genes are linked to FAO. These data suggest that inherent differences in MSC differentiation and FAO may be associated with DNA methylation patterns in infant MSCs and may be one mechanism for developmental programming in infants exposed to obesity in utero.

Supported By: National Institutes of Health; The Obesity Society

1325-P

WITHDRAWN

1326-P

Effects of Maternal Diabetes on PGC-1α Expression in Placenta: Role of microRNA-130b

SHAONING JIANG, APRIL M. TEAGUE, JEANIE B. TRYGGESTAD, TIMOTHY J. LYONS, STEVEN D. CHERNAUSEK, *Oklahoma City, OK, Belfast, Ireland*

Diabetes during pregnancy increases the risk for offspring to develop type 2 diabetes and other metabolic disorders. Abnormal placental function in maternal diabetes affects fetal growth and may predispose offspring to metabolic disease in later life. However, the precise mechanisms through which diabetes during pregnancy impacts placental function remain largely unknown. MicroRNAs are small non-coding RNAs regulating abundance of proteins involved in physiological and pathological cellular processes. Previous studies in our laboratory demonstrated that expression of miR-130b-3p is increased in human umbilical vein endothelial cells from offspring of diabetic mothers. The present study examined the regulation of miR-130b-3p expression as well as key downstream signaling molecules. miR-130b-3p is implicated in the pathogenesis of obesity and T2DM by directly down-regulating peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), a key regulator of mitochondrial energy metabolism. To assess the impact of maternal DM *in vivo*, we quantified PGC-1α by Western blotting of protein extracts from the fetal side of placentae from 24 control and 21 dysglycemic pregnancies. We found PGC-1α was decreased by 40% in human placentae from diabetic mothers compared to healthy controls ($p < 0.05$). In cultured BeWo cells (a human placental trophoblastic cell line), the expression and exosomal secretion of miR-130b-3p were increased by exposure to high glucose (42 mmol/L) commensurate with 40% reduction ($p < 0.01$) in protein abundance of PGC-1α. In addition, overexpression of miR-130b-3p reduced abundance of PGC-1α protein ($p < 0.05$), whereas inhibition of miR-130b-3p increased PGC-1α expression in BeWo cells ($p < 0.05$). These findings reveal a role for glucose regulation of miR-130b-3p expression in modulating PGC-1α expression, which may contribute to abnormal placental mitochondrial function in response to maternal diabetes and potentially affect offspring long-term health.

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1327-P

Placental Triacylglycerol Content Is Higher in Preeclampsia and Is Associated with Maternal Plasma Triacylglycerol Levels

DILYS J. FREEMAN, SAMUEL R. EATHER, ANDREW MCNAIR, SIMON H.J. BROWN, TODD W. MITCHELL, BARBARA J. MEYER, *Glasgow, United Kingdom, Wollongong, Australia*

Maternal obesity and gestational diabetes mellitus are risk factors for preeclampsia (PE) potentially via disordered lipid metabolism. Impaired adipocyte expandability and increased lipolysis leads to excessive fatty acid release. We aimed to determine whether this results in placental ectopic fat accumulation. PE (n=22), defined by ISSHP criteria, and healthy (n=68) pregnant women were recruited in the 3rd trimester. Placental lipid content was determined by quantitative lipidomics using nano-electrospray mass spectrometry. Placental gene expression relative to *TOP1* was quantitated using RT-PCR. Plasma VLDL was isolated by density ultracentrifugation. Plasma and VLDL apolipoprotein B (apoB), triacylglycerol (TAG), total and free cholesterol (cholesteryl ester (CE) calculated by difference) were quantitated on an autoanalyser. PE placenta had higher neutral lipids than controls; TAG mean (SD) 0.27 (0.12) vs. 0.20 (0.11), p=0.001 and CE 0.42 (0.16) vs. 0.31 (0.10), p=0.004, umol/g tissue. *FASN* [69 (45) vs. 42 (28)%, p=0.005], *SREBF1* [70 (22) 40 (18)%, p<0001] and *DGAT 2* [1.38 (1.28) vs. 0.90 (0.76)%, p=0.032] expression relative to *TOP1* was higher in PE than control placenta. Placental TAG correlated with *DGAT2* p (r=0.39, p<0.001) and placental CE with *FASN* expression (r=0.28, p=0.006). Maternal plasma TAG correlated with placental TAG in control (r=0.26, p=0.032) and PE (r=0.41, p=0.051). VLDL particle number, assessed by apoB content, was higher in PE than controls (0.33 vs. 0.19 g/L, p<0.001), and plasma VLDL TAG was higher in PE (1.6 vs. 0.9 mmol/L, p<0.001). VLDL particle lipid composition did not differ. We provide evidence for ectopic fat in placenta. Higher placental TAG in PE is related to higher maternal plasma TAG carried by more VLDL particles, rather than increased *de novo* lipogenesis. *DGAT2* may direct TAG to a potentially harmful lipid pool which in other tissues is associated with insulin resistance.

1328-P

Betaine Supplementation Reduces Placental Glucose and Fatty Acid Transport in a Mouse Model of Maternal High-Fat Feeding

XINYIN JIANG, ESTHER GREENWALD, JUHA NAM, TAMARA AJEEB, *New York, NY*

Maternal high-fat feeding in mice results in hyperglycemia and glucose intolerance during gestation which resembles characteristics of gestational diabetes mellitus (GDM). Betaine is a dietary bioactive compound that serves as a methyl donor, participates in energy metabolism, and influences insulin signaling. In this study, we fed female C57BL/6J mice with either a low-fat or a high-fat diet and provided them with either 85 mM of betaine or control drinking water before and during gestation, to examine the effect of betaine supplementation on maternal and fetal outcomes. High-fat fed mice demonstrated higher weight gain, higher abdominal fat weight, and worse glucose tolerance at mid-gestation (embryonic day E12.5), which were not improved by betaine supplementation. However, Betaine supplementation decreased placental mRNA and protein expression of glucose transporter 1 (Glut1), fatty acid transporter 1 (Fatp1) and fatty acid translocase (Cd36) compared to high-fat control animals. Expression of insulin-like growth factor 2 (Igf2) which promotes placental growth and macronutrient transport was also down-regulated in placentas from betaine-supplemented dams. As a result, placental triglyceride accumulation, as well as placental and pup weight of betaine-supplemented dams were lower than high-fat control dams and were comparable to low-fat dams. In addition, high-fat betaine-supplemented embryos had lower mRNA expression of phosphoenolpyruvate carboxykinase (Pepck) and peroxisome proliferator-activated receptor alpha (Ppara) than high-fat control embryos. In summary, betaine supplementation may prevent placental and fetal overgrowth by reducing placental glucose and fatty acid transport in a mouse model of maternal high-fat feeding and GDM.

Supported By: National Institutes of Health

1329-P

Maternal High-Fat Diet Modulates Glucose Homeostasis and Inflammation by Targeting MicroRNAs in the Early Life of Offspring

JIA ZHENG, XINHUA XIAO, QIAN ZHANG, MIAO YU, *Beijing, China*

Substantial studies indicated that maternal nutrition could determine the susceptibility to obesity, insulin resistance and type 2 diabetes in the adulthood. There is also considerable evidence to suggest that epigenetic modifications may be important molecular basis of malnutrition during early life and glucose metabolism disorders in later life. However, little information is known about the effects and epigenetic programming of maternal malnutrition in the early life of offspring. We examined the effects on the C57BL/6J mice offspring at weaning from dams fed with a high-fat diet (HFD) or normal chow diet throughout pregnancy and lactation. MiRCURY LNATM microRNA Array, qRT-PCR, immunohistochemistry and western blotting were performed in the liver tissues of the offspring. At weaning, the HFD offspring had heavier body weight (P<0.05). The blood glucose levels of HFD offspring were significantly higher at 30 min (P<0.001) and 60 min (P<0.01) after intraperitoneal glucose administration. The HOMA-IR was significantly higher in HFD offspring (P<0.05). Furthermore, the serum interleukin 6 (IL6) and tumor necrosis factor- a (TNF-a) levels were significantly elevated in HFD offspring (P<0.05). Bioinformatic analyses indicated that miR-615, miR-3079, miR-124-5p and miR-101b were significantly down-regulated, while miR-143 were up-regulated in HFD offspring at weaning (Ifold changel≥4, P<0.05). Through target gene analysis and verification, we found the expression of proinflammatory cytokines (IL6 and TNF) and mitogen activated protein kinase 1 (MAPK1) were increased in HFD offspring. In conclusion, it indicated that maternal HFD predisposed to obesity, impaired glucose tolerance and insulin resistance in the early life of offspring. Our study was novel in showing that the potential mechanisms that influenced this phenotype may be related partially to up-regulate proinflammatory cytokines by targeting certain miRNAs in the offspring.

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1330-P

Persistent Changes in Methylation in Offspring Exposed to Intrauterine Hyperglycemia

RONALD C. MA, JU LUAN, GRACE CHEUNG, CADMON K. LIM, YING WANG, HEUNG MAN LEE, GREG E. TUTINO, CLAUDIA H. TAM, WING YEE SO, JULIANA C.N. CHAN, WING HUNG TAM, *Hong Kong, China*

Offspring exposed to maternal diabetes have increased risk of obesity, diabetes, and hypertension, and epigenetic changes are implicated. We performed epigenome-wide methylation analysis using a prospective cohort of offspring of mothers with or without gestational diabetes (GDM) who have been followed-up for 22 years. We included 47 offspring (23 mothers with NGT+24 mothers with GDM/GIGT, diagnosed by WHO 1998 criteria). Compared with offspring of mothers with NGT (ON), offspring of mothers with GDM (OGDM) had significantly higher diastolic BP (p<0.001) and lower HDL-C levels (p=0.008) at 8-year follow-up, and significantly higher BMI (p=0.009), higher blood glucose, and significantly higher insulin levels at 15-year. Genomic DNA was extracted from 94 blood samples collected from the 47 offspring at the 8-year and 15-year evaluation, respectively. Genome-wide DNA methylation status was studied using the HumanMethylation 450K BeadChip (Illumina Inc, U.S.). After quality control, normalization, removal of SNP-enriched sites and probes on sex chromosomes, 451,661 probes were retained for further analysis. The beta value (β) was used to estimate the methylation level of the CpG locus using the ratio of intensities between methylated and unmethylated alleles. A significant difference in methylation was defined as false discovery rate (FDR)-corrected Diff Score ≥ 13 ~ P ≤ 0.05. Differential methylated CpG sites and regions (tiling, promoter, gene and CpG islands) among ON and OGDM were studied using RnBeads or by two-sided Welch t-test, while comparisons of paired samples between 8-year and 15-year follow-ups were analyzed by paired Student t-test. We identified several regions of differential methylation, with a marker on chrm9 being the top site for increased methylation in OGDM (p=4.6 x 10^{-5}). The top 20 differential methylated CpG sites were selected for validation. Our findings suggest presence of persistent methylation changes in offspring exposed to maternal hyperglycaemia.

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1331-P

Comparison of DNA Methylation Profiles in Sib-Pairs Discordant for Intrauterine Exposure to Maternal Gestational Diabetes Mellitus

SOO-HEON KWAK, EUNAE KIM, JAE HYUN BAE, MYOUNG JIN JI, SUNG HEE CHOI, KYONG SOO PARK, JOOHUN SUNG, HAK C. JANG, *Seoul, Republic of Korea, Seongnam, Republic of Korea*

Offspring of women with a history of gestational diabetes (GDM) is at significantly increased risk for developing obesity and diabetes. It is suggested that intrauterine hyperglycemia can induce epigenetic changes in fetus which might result in detrimental effect on future metabolic phenotypes. In this study, we compared pair-wise DNA methylation status between siblings whose intrauterine exposure to maternal GDM are discordant.

A total of 19 sib-pairs born from 18 Korean women who experienced both normal pregnancy and GDM pregnancy were included. DNA was extracted from peripheral leukocytes when the offspring were at age between 4 and 15 years. An epigenome-wide association study was conducted using Illumina Infinium HumanMethylation 450 BeadChip assays. Differential methylation was compared within each sib-pairs discordant for GDM pregnancy.

In the unsupervised clustering based on Manhattan distance, 33 samples were closely related to intrauterine GDM status. A total of six CpG sites were differential methylated within sib-pairs with false discovery rate of less than 0.1 (P < 1.50 x 10^{-6}). The six sites were located in MFHAS1, LOC92973, PACRG, HNF4A, PITPNM3, and RREB1. Among these CpG sites, cg08407434 which is located at HNF4A was consistently hypermethylated in offspring of GDM with mean pairwise difference methylation of 1.3% (P = 9.10 x 10^{-7}). Using Ingenuity pathway analysis of differentially methylated regions, we found that immune response was overrepresented by hypermethylated genes.

To the best of our knowledge, this is the first study to investigate the epigenome-wide difference in methylation within sib-pairs discordant for intrauterine hyperglycemia. We found several suggestive CpG sites with differential methylation, including the one located in HNF4A which warrants further investigation.

1332-P

Elevated Urinary NGAL during the First Trimester of Pregnancy Predicts Preeclampsia in Women with Type 1 Diabetes

MICHELLE B. HOOKHAM, CLARE B. KELLY, JEREMY Y. YU, ALICIA J. JENKINS, ALISON NANKERVIS, KRISTIAN F. HANSSEN, SATISH K. GARG, JAMES A. SCARDO, SAMAR M. HAMMAD, DONGXU FU, CHRISTOPHER E. ASTON, TIMOTHY J. LYONS, *Belfast, United Kingdom, Sydney, Australia, Melbourne, Australia, Oslo, Norway, Aurora, CO, Spartanburg, SC, Charleston, SC, Oklahoma City, OK*

The prevalence of preeclampsia (PE) is increased 4-5 fold by maternal type 1 diabetes mellitus (T1DM). Neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of proximal renal tubule dysfunction, has shown promise as a predictive marker for PE in the general population. We investigated the utility of urinary and plasma NGAL in predicting PE in T1DM women. Using samples from an established, prospective, complication-free (specifically no microalbuminuria, no hypertension) cohort of T1DM women, maternal urinary and plasma NGAL levels were measured by ELISA in samples obtained at three study visits (V1: 12.4±1.8, V2:21.7±1.4, and V3:31.4±1.5 weeks gestation (mean±SD)) in 21 T1DM women who subsequently developed PE (DM+PE+), 24 T1DM women who remained normotensive (DM+PE-), and 19 normotensive, nondiabetic women (DM-, reference controls). The diabetic groups were matched for age, diabetes duration, HbA1c, and parity. All subjects were complication-free before pregnancy, and all study visits preceded clinical onset of PE. Urinary NGAL (creatinine-corrected, uNGALcc) increased with gestation in each group (p<0.01), and was significantly elevated at V1 in DM+PE+ vs. DM+PE- (26.2 (20.0-34.4) vs. 16.7 (13.3-21.1) (geometric mean (95% CI)), p= 0.01), with similar trends at V2 and V3. Combined with simple clinical data (BMI, HbA1c, total daily insulin dose) in logistic regression analysis, uNGALcc improves prediction of PE at V1 (p=0.049): area under receiver operator characteristic curve: 0.90. Plasma NGAL did not predict PE at any visit. The data suggest that uNGALcc may have clinical utility for prediction of PE in T1DM women. First trimester subclinical renal tubular injury may predispose T1DM women to PE.

1333-P

Maternal Circulating Adipokine and Cytokine Concentrations in Normal Pregnancy and Gestational Diabetes

XINHUA CHEN, THERESA SCHOLL, *Stratford, NJ*

We examined whether maternal circulating adipokines (adiponectin and resistin) and cytokines (IL-6, 8, 10, TNF-α and GMCSF) are different in women who developed gestational diabetes mellitus (GDM) or mild hyperglycemia non-GDM when compared to normal pregnant women. Data are longitudinal and from a large prospective cohort study - the Camden study.

Data from n=1,886 pregnant women were examined (African-American 37%, Hispanic 48%, Caucasian 15%, age 22.1±5.2 (yr.), pregravid BMI (kg/m^2) 25.7±6.3). Serum adipokines and cytokines at entry (week 16) and the 3rd trimester (week 30) were assayed by multiplex on the Magpix system using Luminex xMAP technology. All results were adjusted for maternal age, BMI, parity, cigarette smoking and ethnicity.

At entry, the adiponectin level (log transformed mean ± log SE) was significantly lower in women later diagnosed with GDM (n=84, 1.08±0.03) and those with positive glucose challenge test (GCT) non-GDM (n=140, 1.15±0.01) than women with a normal GCT (controls, n=1,662, 1.19±0.01, p for trend <0.0001). The differences in resistin and other cytokines among the 3 groups were not significant. During the 3rd trimester, adiponectin differences remained the same as at entry. In addition, IL-8 and TNF-α (log mean ± log SE) were significantly increased in GDM and/or positive GCT non-GDM vs. controls (p for trend <0.01 for each). The ratio of IL-8/IL10 was 11.13±2.01, 5.24±1.52, 3.62±0.44 in GDM, positive GCT non-GDM and controls respectively (p for trend <0.001). Similar results were found in the ratios of IL-6/IL10 (p<0.01) and TNF-α/IL10 (p<0.0001).

These observations suggested that deficiencies in adiponectin, a strong anti-inflammatory marker, exist prior to the diagnosis of GDM and mild hyperglycemia non-GDM. Differences in cytokines (IL-6, 8 and TNF-α) and their ratios with IL-10 detected during later pregnancy implicate an imbalance in the inflammatory and anti-inflammatory response to the development of impaired glucose metabolism.

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1334-P

Impact of Maternal Glucose and BMI on Offspring Cardiometabolic Outcomes: A 22-Year Follow-up Study

GREG E. TUTINO, CLAUDIA H.T. TAM, RISA OZAKI, WING YEE SO, MICHAEL H.M. CHAN, GARY T.C. KO, ALICE KONG, DALJIT S. SAHOTA, XILIN YANG, JULIANA C.N. CHAN, WING HUNG TAM, RONALD C.W. MA, *Hong Kong, China*

Offspring of pregnancies complicated by gestational diabetes (GDM) and overweight/obesity (OwOb) are at increased risk for cardiometabolic disorders. We examined the risk of developing diabetes (DM) and OwOb in offspring of Chinese women with a history of GDM and characterized the association between maternal glycaemia and BMI during pregnancy with long term outcomes in offspring. Subjects were identified from a consecutive cohort of women recruited from 1992-1994 who underwent GDM screening between 24-28 weeks gestation. Subjects and offspring were recalled for follow up with detailed evaluation including multipoint OGTT at 8, 15 and 22 years. Logistic regression was used to estimate the risk of offspring developing DM and OwOb at follow up. Linear regression was applied to estimate the association between measures of maternal glucose and adiposity at pregnancy with cardiometabolic indices in offspring. Beta cell function was evaluated using the oral disposition index and trajectory of beta cell function was calculated at 22 years. Included in the analysis were 112 offspring, 57 male, with a mean age of 22.0 years. A combination of DM/impaired glucose tolerance was found in 7/112 (6.3%). The OwOb percentage was 37.1% including 59.6% of offspring with maternal BMI≥23 at pregnancy compared to 18.8% with BMI<23 (p<0.001). Offspring from a high BMI pregnancy have an odds ratio of 5.99 (95% CI 2.44-14.68) for BMI≥23 at follow up compared to those with maternal BMI<23 after adjusting for confounders (p<0.001). Maternal prepregnancy BMI was strongly associated with offspring fasting, AUC glucose, BMI, visceral fat rating, SBP, and TG at follow up (p value <0.001 to 0.041). Neither fasting nor 2 hr glucose during pregnancy was associated with offspring glycaemic or adiposity indices at follow up after adjustment for confounders. Offspring of women with a high prepregnancy BMI have a high prevalence of OwOb at 22 years follow-up and are at substantial increased risk for related comorbidities.

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1335-P

The Influence of Gestational Diabetes on Fetal and Maternal Heart Rate Variability during an Oral Glucose Tolerance Test

ELLEN FEHLERT, KATRIN WILLMANN, LOUISE FRITSCHE, KATARZYNA LINDER, HALIZA MAT HUSIN, FRANZISKA SCHLEGER, HANS-ULRICH HÄRING, HUBERT PREISSL, ANDREAS FRITSCHE, *Tübingen, Germany*

Gestational diabetes mellitus (GDM) potentially harms the child before birth and may have consequences later in life. We previously found GDM to be associated with developmental changes in the central nervous system. We now hypothesize that GDM may also impact on the fetal autonomic nervous system. This might be detectable either under rest or under metabolic stress like an oral glucose tolerance test (oGTT). Heart rate variability (HRV) is an accepted diagnostic and prognostic tool to assess autonomic nervous function. We therefore measured HRV of mothers and fetuses during a 3-point oGTT in women with and without GDM using magnetocardiography. Fetal magnetocardiography (fMCG) is a noninvasive method to detect fetal heart rate patterns with high temporal resolution. The investigated study cohort included forty-nine pregnant women with a gestational age of at least twenty-seven weeks, thirty-six metabolically healthy and thirteen women with GDM. They all underwent the same examination setting with oGTT during which fMCG was recorded three times. Compared to mothers with normal glucose regulation, mothers with GDM showed increased heart rate but no significant differences of maternal HRV. In contrast, HRV in fetuses of mothers with GDM significantly differed from those in the metabolically healthy group at 120 minutes after glucose load regarding standard deviation normal to normal beat (SDNN) (p = 0.012), low frequency band (p = 0.008) and high frequency band (p = 0.031). In conclusion, these results showed an altered response of the fetal autonomic nervous system to metabolic stress in GDM complicated pregnancies. Thus, disturbances in maternal glucose metabolism might not only impact on the central nervous system of the fetus but may also affect the fetal autonomic nervous system. Since both alterations could have consequences in later life, good metabolic control is warranted during pregnancy.

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PREGNANCY—CLINICAL/EPIDEMIOLOGY

Moderated Poster Discussion: Innovative Observations/Predictors of Gestational Diabetes and Maternal Outcomes *(Posters: 1336-P to 1343-P), see page 18.*

1336-P

Dysregulated Hypothalamic-Pituitary-Adrenal Axis (HPA) Is Linked to Glucose Intolerance in Pregnancy: A Likely Mechanism for Increased Risk of Gestational Diabetes (GDM) in South Asians (SA)

HEMA VENKATARAMAN, BRIAN KEEVIL, REBECCA REYNOLDS, PONNUSAMY SARAVANAN, *Coventry, United Kingdom, Manchester, United Kingdom, Edinburgh, United Kingdom*

SA have a higher risk of GDM, type 2 diabetes and metabolic syndrome than white Caucasians (WC). Dysregulated HPA activity is a plausible candidate mechanism. We hypothesised that HPA axis activity is increased in SA pregnancies compared to WC and is associated with hyperglycaemia in pregnancy. We aimed to study the ethnic differences in HPA activity in early pregnancy and test associations with glucose tolerance in later pregnancy.

Methods: The PRiDE-HPA is a sub-study of the PRiDE study - a multicentre high-risk pregnancy cohort. SA and WC women were recruited from the PRiDE study <16 weeks gestation. Saliva was collected at waking, 30 min after, 4pm and bedtime at recruitment along with 24 hour urine. Salivary cortisol and cortisone were analysed using mass spectrometry and urinary glucocorticoid (UGC) analysis using gas chromatography. Analyses were adjusted for BMI, maternal age, smoking and gestation.

Results: 52 SA, 52 WC were recruited. Both waking (β = 1.469, p=0.019) and peak cortisone (30 min) (β 0.591, p=0.035) at 12 weeks independently predicted fasting plasma glucose at 24-28 weeks gestation, after adjustment as above. In the adjusted analysis, SA had higher cortisone awakening response (β =0.40, p=0.034) than WC. UGC analysis indicated that SA had higher 11bHSD2 activity (β = 0.069, p=0.045) and lower 5a-reductase activity (5AR) (β =-0.154, p= 0.013). Despite lower BMI, total UGC excretion in SA was similar to WC. Total UGC excretion correlated positively with BMI only in WC (p=0.02) and to waist circumference (p=0.005) and skin fold thickness (p=0.038) in SA.

Conclusion: Waking and peak salivary cortisone in early pregnancy are independent markers of glycaemia in later pregnancy. SA have higher awakening cortisone responses than WC with increased activation of 11 βHSD and reduced 5AR. Higher HPA activity and dysregulated clearance of cortisol could explain higher risk of GDM in SA.

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1337-P

Shared Genetic Determinants of Glycemic Traits In and Outside of Pregnancy

CAMILLE E. POWE, CATHERINE ALLARD, LUIGI BOUCHARD, PATRICE PERRON, JOSE C. FLOREZ, MARIE-FRANCE HIVERT, *Boston, MA, Sherbrooke, QC, Canada, Cambridge, MA*

We aimed to test whether genetic determinants of glycemic traits outside of pregnancy are associated with glycemic traits in pregnancy. We genotyped 501 pregnant women for single nucleotide polymorphisms (SNPs) associated with glycemic traits in non-pregnant individuals. We built genetic risk scores (GRSs) for fasting glucose (FG) and fasting insulin (FI) based on known genome-wide significant associations in non-pregnant individuals. From the FG and FI loci, we selected SNPs for insulin secretion (IS) and insulin resistance (IR) GRSs based on associations in publicly available MAGIC datasets. We used linear regression to test for associations between GRSs and glycemic traits at 24-30 weeks gestation, assuming additive genetic models, with multivariate adjustment (MVA) for BMI, maternal age, and gestational age. We tested for associations between GRSs and gestational diabetes mellitus (GDM) with logistic regression. We found that the FG GRS (23 SNPs) predicted FG in pregnant women (β=0.54 representing the increase in FG in mg/dL per risk allele carried, P<0.001); this was not attenuated by MVA. The IS GRS (7 of 23 FG SNPs) predicted insulin secretion (β=-0.02 representing the decrease in natural log transformed (ln) Stumvoll 1st phase estimate per risk allele, P=0.02), without attenuation by MVA. The FI GRS (18 SNPs) did not predict FI (β=0.01 representing the increase in ln FI in µU/ml per risk allele, P=0.19 with MVA). The IR GRS (8 of 18 FI SNPs) predicted IR (β=-0.04 representing the decrease in ln Matsuda sensitivity index per risk allele, P=0.005), without attenuation by MVA. The FG GRS predicted GDM (OR 1.13 per FG risk allele, P=0.04), while the other GRSs were not associated with GDM (P>0.10). In conclusion, genetic loci associated with FG, IS,

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

and IR in non-pregnant individuals are similarly associated with these traits in pregnant women. In contrast, FI may have a different genetic architecture in pregnancy. Women with GDM have an increased burden of genetic risk alleles associated with elevation of FG.

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1338-P

Seasonal Temperature and the Risk of Gestational Diabetes

GILLIAN L. BOOTH, JIN LUO, RAHIM MOINEDDIN, DENICE S. FEIG, JOEL G. RAY, *Toronto, ON, Canada*

Short-term exposure to cold appears to improve insulin sensitivity in both animal models and in humans, through mechanisms linked to the activation of brown adipose tissue. However, no studies to date have shown a relationship between outside air temperature and the development of a metabolic disease like diabetes. We hypothesized that short-term exposure to cold temperatures during the second trimester of pregnancy might lead to a lower risk of gestational diabetes (GDM). We used anonymous, administrative health databases to identify all pregnant women living in Toronto, Canada, and surrounding cities between April 1, 2002 and March 31, 2014 (N=556,750) who were diabetes-free prior to pregnancy. The diagnosis of GDM was based on a validated algorithm that uses diagnostic codes from hospital records and fee-for-service claims submitted by physicians during pregnancy or within 6-months after. Generalized estimating equations (GEE) models were conducted to study the relationship between mean 30-day air temperature level in the period prior to 27 weeks of gestation - as reported by Environment Canada - on the risk of GDM. We found a direct, linear relationship between mean 30-day temperature values and rates of GDM - with no apparent threshold for this effect. The lowest rate of GDM occurred at coldest temperatures; the prevalence was 4.6% at a mean 30-day temperature of ≤-10 Celsius whereas the prevalence rose to 7.7% at a mean 30-day temperature of ≥24 Celsius. On multivariate analysis, there was a significant linear relationship between air temperature and GDM risk after adjusting for maternal age, ethnicity, income, and parity, and year of delivery. For every 10-degree rise in temperature, the risk of GDM rose 6.5% (adjusted OR 1.065, 95% CI 1.053-1.075). In conclusion, our study demonstrated a direct relationship between seasonal temperature and GDM risk. This finding has important implications for the prevention and treatment of diabetes in the setting of pregnancy.

1339-P

The First Trimester: Prediction of Gestational Diabetes

ARIANNE N. SWEETING, GLYNIS P. ROSS, JENCIA WONG, PAUL F. WILLIAMS, MIKKO SAIRANEN, HEIKKI KOURU, JON HYETT, *Sydney, Australia, Turku, Finland*

The best screening test for gestational diabetes (GDM) in early pregnancy is unknown. Screening is currently predominantly based on maternal clinical risk factors however these have a poor positive predictive value. Increasing evidence suggests that maternal biomarkers implicated in GDM can be identified in the first trimester. Combining these maternal clinical characteristics and biomarkers may improve GDM risk prediction in early pregnancy. Our objective was to develop a risk prediction algorithm for GDM at $11\text{-}13^{+6}$ weeks' gestation using a combination of maternal clinical and biomarker data in a large metropolitan multi-ethnic Australian population. Maternal clinical data at the time of aneuploidy (nuchal) screening from 224 women who developed GDM and 718 controls were collected prospectively. Biomarkers (β-HCG, PAPP-A, non-fasting glucose and lipids, adiponectin, leptin, PAI-2 and lipocalin-2) were measured on retrieved samples**.** Independent GDM predictors were determined from stepwise regression analyses and the best performing combination calculated by area under the receiver-operating characteristic curves (AUC-ROC). The AUC-ROC for traditional maternal clinical risk factors (age>35 years, BMI>30kg/m^2, south/east Asian ethnicity, past history of GDM and family history of diabetes) was 0.72. This improved to 0.93 with the addition of maternal mean arterial pressure (MAP), PAPP-A, triglycerides and lipocalin-2 for a detection rate of 87% (20% false positive rate). Our algorithm accurately predicts GDM in early pregnancy through the addition of routine and novel biomarkers to traditional maternal clinical risk factors. Future research should prospectively validate these findings and assess early intervention and preventive strategies to reduce the burden of GDM.

1340-P

A Prospective Study of Body Iron Stores in Pregnancy and Risk of Gestational Diabetes: Findings from a Multiracial Cohort

SHRISTI RAWAL, WEI BAO, YEYI ZHU, STEFANIE N. HINKLE, JAGTESHWAR GREWAL, PAUL ALBERT, MICHAEL Y. TSAI, CUILIN ZHANG, *Rockville, MD, Iowa City, IA, Minneapolis, MN*

Oxidative stress from high body iron stores has been implicated in the pathogenesis of type 2 diabetes. Yet, studies examining longitudinal changes in iron status during pregnancy and their role in the development of gestational diabetes (GDM), especially by utilizing novel biomarkers like hepcidin, are few and inconsistent. We aimed to prospectively address these data gaps in a nested GDM case (n=107)-control (n=214) study (matched 1:2 on age, race/ethnicity, and gestational age at blood draw) within the multiracial NICHD Fetal Growth Study. GDM diagnosis was based on medical record review. Plasma ferritin, soluble transferrin receptor (sTfR) and hepcidin were measured at two visits prior to GDM diagnosis (gestational weeks (GW) 8-13 and 16-22), as well as at GW 24-29 and 34-37. Adjusted odds ratios (aORs) [95% confidence intervals (CIs)] for GDM were estimated using conditional logistic regression adjusting for demographics, pre-pregnancy BMI, C-reactive protein, and other major risk factors. Ferritin and hepcidin levels declined whereas sTfR concentrations increased as the pregnancy progressed. Ferritin levels were significantly higher among women who subsequently developed GDM than those who didn't and were positively related to GDM risk; aOR (95% CI) comparing the highest vs. lowest quartile of ferritin was 2.55 (1.18, 5.54) during GW 8-13 and 4.50 (1.53, 13.2) during GW 16-22. Hepcidin levels were significantly higher in GDM than non-GDM women and were positively related to GDM risk during GW 16-22 but not earlier; aOR (95% CI) comparing the highest vs. lowest quartile was 2.58 (1.06, 6.29). In contrast, ratio of sTfR to ferritin, an indicator of iron deficiency, was significantly and inversely associated with GDM risk; aOR (95% CI) comparing the highest vs. lowest quartile was 0.29 (0.12, 0.72) at GW 8-13 and 0.14 (0.04, 0.44) at GW 16-22. Our data suggest that high maternal iron stores may play a role in the pathogenesis of GDM starting from early pregnancy.

1341-P

Targeted Metabolomics Demonstrates Distinct and Overlapping Maternal Metabolomes Associated with BMI and Glucose during Pregnancy across Four Ancestry Groups

WILLIAM L. LOWE, JAMES BAIN, MICHAEL MUEHLBAUER, ANNA REISETTER, MICHAEL NODZINSKI, SAYA JACOB, ROBERT STEVENS, OLGA ILKAYEVA, LYNN P. LOWE, CHRISTOPHER B. NEWGARD, BOYD E. METZGER, DENISE SCHOLTENS, *Chicago, IL, Durham, NC*

Maternal hyperglycemia and obesity during pregnancy are associated with adverse newborn outcomes. The impact of maternal phenotypes on fetal phenotypes can be characterized using metabolomics. As maternal hyperglycemia and obesity have independent effects on fetal adiposity, we used serum and phenotype data from the Hyperglycemia and Adverse Pregnancy Outcome Study to address the hypothesis that maternal glycemia and BMI have distinct metabolic profiles. Fasting and 1-hr serum samples obtained during an oral glucose tolerance test at 28 weeks gestation were analyzed using targeted metabolomics to measure amino acids and acylcarnitines (AC) via mass spectrometry and conventional clinical metabolites in 1600 mothers, 400 each of Afro-Caribbean, Northern European, Mexican-American, and Thai ancestry. After adjusting for maternal BMI, 23 fasting metabolites were significantly associated with maternal fasting plasma glucose (FPG, $p < 9 \times 10^{-4}$). Of these, only glutamine/glutamate was also associated with maternal BMI after adjusting for maternal FPG. AC of medium- and long-chain fatty acids (FA) were negatively associated with FPG but positively associated with BMI. In contrast, of the 30 1 hr maternal metabolites associated with 1 hr glucose, 17 were significantly associated with BMI, including 3-hydroxybutyrate, AC of medium- and long-chain FA, leucine/isoleucine, glutamine/glutamate, asparagine/aspartate and phenylalanine. Associations of maternal metabolites with newborn phenotypes were limited. Maternal fasting and 1 hr triglycerides were significantly associated with sum of skinfolds, while maternal 1 hr methionine and alanine were associated with birth weight. In conclusion, maternal glycemia and BMI have both distinct and similar metabolic signatures depending upon the metabolic state of the mother, although few of these metabolites demonstrate association with newborn phenotypes.

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1342-P

Relationship between Maternal Glycaemic Indices and Measures of Adiposity during Pregnancy with Long-Term Cardiometabolic Risk: A 22-Year Follow-up Study

GREG E. TUTINO, CLAUDIA H.T. TAM, RIZA OZAKI, WING YEE SO, MICHAEL H. CHAN, GARY T.C. KO, ALICE P.S. KONG, DALJIT SAHOTA, XI L. YANG, JULIANA C.N. CHAN, WING HUNG TAM, RONALD C. MA, *Hong Kong, China*

Women with a history of gestational diabetes mellitus (GDM) are at increased risk for later type 2 diabetes (T2D). We examined the risk of developing impaired glucose tolerance (IGT)/T2D and metabolic syndrome (MetS) in Chinese women with a history of GDM and characterized the association between maternal glycaemia during pregnancy with long-term outcomes. Subjects were identified from a consecutive cohort of 1032 women recruited from 1992-1994 who underwent GDM screening between 24-28 weeks gestation. Subjects and offspring were recalled for follow up with detailed evaluation including multipoint OGTT at 8, 15 and 22 years. Logistic regression was used to estimate the risk of developing IGT/T2D and MetS at follow up. Linear regression was applied to estimate the association between maternal glycaemia at pregnancy and follow up. Beta cell function was evaluated using the oral disposition index and trajectory of beta cell function was calculated at 22 years. Included in the analysis were 121 women with a mean follow up of 22.5 years, mean age of 50.3 years. DM or IGT was present in 47.1% of women with GDM history compared to 27.8% among those negative at baseline (p=0.047). GDM was associated with an odds ratio of 2.48 (95% CI 1.03-5.99) for combined DM/IGT at follow up after adjusting for confounders (p=0.04). Women with a prepregnancy BMI≥23 had an odds ratio of 5.43 (95% CI 1.87-15.72) for MetS at follow up compared to those with BMI<23 (p=0.002). Both fasting and 2 hr glucose during pregnancy were strongly associated with glycaemic indices at follow up (p value <0.001 to 0.016). Beta cell function deteriorated progressively after GDM. Chinese women with a history of GDM have a high prevalence of DM/IGT at 22 years follow up. Glucose levels during mid-pregnancy are strongly associated with those of middle age and highly predictive of future dysglycaemia. A high prepregnancy BMI confers substantial risk for the subsequent development of MetS.

Supported By: Research Grants Council of Hong Kong

1343-P

A Prospective Study of Insulin-like Growth Factor 1 and Binding Proteins 2 and 3 and Risk of Gestational Diabetes

YEYI ZHU, PAULINE MENDOLA, PAUL ALBERT, WEI BAO, MICHAEL Y. TSAI, CUILIN ZHANG, *Rockville, MD, Iowa City, IA, Minneapolis, MN*

Insulin-like growth factor (IGF)-axis may be implicated in glucose metabolism and homeostasis. Data on longitudinal changes in IGF-axis biomarkers throughout pregnancy and their roles in gestational diabetes (GDM) development are lacking. We prospectively investigated the roles of IGF-I and IGF binding proteins (IGFBP)-2 and -3 in the etiology of GDM. In a nested case-control study within the NICHD Fetal Growth Study, 107 GDM cases were identified by medical record review and matched 1:2 to non-GDM controls on age, race/ethnicity, and gestational week (GW) at blood draw. Plasma concentrations of IGF-I, IGFBP-2, and IGFBP-3 were measured at GW 8-13, 16-22, 24-29, and 34-37. Conditional logistic regression was used, adjusting for major risk factors including pre-pregnancy body mass index. Overall, IGF-I and IGFBP-3 levels and IGF-I/IGFBP-3 ratio increased whereas IGFBP-2 levels decreased as pregnancy progressed among both cases and controls. The mean levels of IGF-I and IGF-I/IGFBP-3 ratio were significantly higher whereas IGFBP-2 levels were significantly lower in cases than controls during pregnancy before GDM diagnosis. After adjustment for major risk factors, there was a 2.93-fold (95% CI 1.18-7.30) increase and 96% (95% CI 84-99%) decrease in risk of GDM comparing the highest vs. lowest quartile of IGF-I and IGFBP-2 concentrations, respectively, at GW 8-13. IGFBP-3 concentrations were not associated with GDM risk. Similar results were observed at GW 16-22. Further, IGFBP-2 significantly improved the prediction accuracy of GDM over conventional risk factors plus plasma glucose levels (area under the curve: 0.71 vs. 0.62 at GW 8-13 P = 0.001; 0.72 vs. 0.68 at GW 16-22, P = 0.021). The findings suggest that IGFBP-2 might serve as a novel and early marker for GDM, independent of conventional risk factors and plasma glucose levels. Moreover, metabolic perturbations of the IGF-axis might be underway at GW 8-13, about 11-15 weeks earlier before GDM is typically screened for.

Moderated Poster Discussion: Novel Insights into Complications, Treatments, and Offspring Outcomes in Diabetes and Pregnancy *(Posters: 1344-P to 1351-P), see page 17.*

1344-P

Serum FABP4 Predicts Preeclampsia in Pregnant Women with Type 1 Diabetes

AMY C. WOTHERSPOON, VALERIE A. HOLMES, CHRIS C. PATTERSON, IAN S. YOUNG, DAVID MCCANCE, DAPIT STUDY GROUP, *Belfast, United Kingdom, Belfast, Ireland*

Preeclampsia is a life threatening illness that can occur during pregnancy. It is defined as new onset hypertension and proteinuria occurring after 20 weeks gestation and affects between 2 and 8% of women. Women with diabetes are 2 to 4 times more likely to develop preeclampsia than the general maternal population. Fatty Acid Binding Protein-4 (FABP4) has been identified as a possible biomarker to predict preeclampsia. The aim of this study was to determine if FABP4 predicts preeclampsia in women with type 1 diabetes. FABP4 was measured by ELISA (Biovendor, Modrice, Czech Republic) in a total of 1,293 serum samples collected from 710 women with type 1 diabetes who took part in the Diabetes and Preeclampsia Intervention Trial (DAPIT). FABP4 levels were measured at randomisation (8-22 weeks) and at 26 weeks (± 2 weeks) gestation. Overall, 120 women developed preeclampsia (17%). Maternal serum concentrations of FABP4 were significantly elevated ($p<0.05$) at both time points in women who later developed preeclampsia (median [IQR] - 15.9 [11.6-21.4] ng/ml vs. 12.7 [9.6-17.0] ng/ml at 8-22 weeks and 18.8 [13.9-26.0] ng/ml vs. 14.5 [10.8-19.6] ng/ml at 26 weeks). Women who were primiparous, overweight or had a history of preeclampsia were more likely to develop preeclampsia ($P<0.05$), and had elevated diastolic and systolic blood pressure and HbA1c values at randomisation. FABP4 correlated with BMI, systolic and diastolic blood pressure at both time points ($P<0.05$). Logistic regression analysis produced an OR for preeclampsia of 1.7 (95% CI: 1.2, 2.4) at randomisation and OR 1.7 (95% CI: 1.2, 2.5) at 26 weeks as for each doubling of FABP4 concentration after adjusting for these and other potential confounders. Serum FABP4 measured in both first and second trimester predicts preeclampsia in women with type 1 diabetes independently of established risk factors.

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1345-P

Nonalcoholic Fatty Liver Disease Is Associated with Gestational Diabetes Mellitus and Abnormal Postpartum Glucose Metabolism

MARYAM SATTARI, FERNANDO BRIL, ROBERT S. EGERMAN, KENNETH CUSI, *Gainesville, FL*

Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide. The metabolic consequences of NAFLD in specific populations, such as pregnancy remain elusive. The aim of this study was to evaluate the association between NAFLD and the development of gestational diabetes mellitus (GDM) as well as postpartum defects in glucose and lipid metabolism. To this end, we recruited 32 pregnant women from the general population and performed: 1.) a liver ultrasound during the last trimester and/or early postpartum period to establish the diagnosis of NAFLD; and 2.) fasting and postprandial (75-gram oral glucose tolerance test) plasma glucose, insulin, C-peptide, and FFA at 6 weeks postpartum to determine insulin secretion and insulin resistance. The prevalence of NAFLD was high (22%) and could not be predicted on clinical characteristics such as age, ethnicity, systolic or diastolic blood pressure, except for patients with NAFLD being on average more obese ($p<0.01$). Patients with NAFLD had a 3-fold higher prevalence of GDM (71% vs. 24%, p=0.03), that was independent of other relevant clinical variables and not fully accounted for by the greater degree of adiposity. At 6 weeks postpartum, fewer patients with GDM and NAFLD demonstrated normal glucose tolerance vs. those without NAFLD (40% vs. 67%). Patients with NAFLD continued to have a worse metabolic profile than patients without NAFLD, including a trend towards higher fasting insulin (10±1 vs. 7±1 μIU/ml, p=0.08), lower plasma HDL-C (42±5 vs. 52±4 mg/dl, p=0.09) as well as worse hepatic (HOMA-IR: 2.2±0.3 vs. 1.6±0.2, p=0.07) and adipose tissue (Adipo-IR_{index}: 3.8±1.0 vs. 2.5±0.3 μIU · mmol/L, p=0.12) insulin resistance.

Conclusion: NAFLD is common during pregnancy and is associated with an unfavorable postpartum metabolic profile. Screening for NAFLD during pregnancy and/or postpartum period could help identify patients at future high-risk of developing T2DM.

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For author disclosure information, see page A696.

1346-P

Closed-Loop Insulin Delivery in the Intrapartum and Early Postpartum Period in Women with Type 1 Diabetes in Pregnancy

ZOE A. STEWART, M.E. WILINSKA, SARA HARTNELL, DAVID SIMMONS, ROSEMARY TEMPLE, KATHARINE STANLEY, GERRY RAYMAN, ROMAN HOVORKA, HELEN R. MURPHY, *Cambridge, United Kingdom, Norwich, United Kingdom, Suffolk, United Kingdom*

Intrapartum glucose control is widely considered an important predictor of neonatal hypoglycaemia in women with diabetes in pregnancy. For women with type 1 diabetes, insulin is delivered either using variable rate intravenous infusion, multiple daily injections, or pump therapy during the intrapartum and early postpartum periods. However, maternal glucose control is often suboptimal with frequent intrapartum hyperglycaemia and postpartum hypoglycaemia. Neonatal hypoglycaemia remains common. Closed-loop insulin delivery may be able to improve glucose control and reduce health professional intervention.

We present glucose data from the first 14 women with type 1 diabetes to use closed-loop insulin delivery during labour and delivery (age 34.7±4.7 yrs, diabetes duration 24.8±6.8 yrs, early pregnancy HbA1c 50.8±6.0 mmol/mol; mean ±SD). Median gestation at delivery was 36.9 wks (range 28+4-38+4). 1 woman delivered vaginally, 4 via caesarean section after onset of labour, and 9 via caesarean section before labour (including 2 under general anaesthetic). Median (interquartile range [IQR)] birthweight was 3588 (2733,3971) g. In the 24 hours prior to delivery, participants had a mean glucose of 6.2 (5.8, 7.3) mmol/L, and spent 82.7 (54.2, 94.4)% of time with target glucose values (3.5-7.8 mmol/L), and 0.8 (0, 2.2)% time below 3.5 mmol/L; median (IQR). In the first 48 hours post-delivery, women had a mean glucose of 6.5 (5.8, 7.2) mmol/L, and spent 74.6 (59.4, 87.5)% time in target, and 0 (0, 0.5)% time below 3.5 mmol/L. Peak intrapartum glucose and glucose at delivery were 9.6 (8.6, 12.1) and 6.7 (6.3, 7.2) mmol/L respectively; median (IQR). There were no episodes of hypoglycaemia <2.2mmol/L.

Closed-loop insulin delivery appears safe and efficacious during the intrapartum and early postpartum periods for women with type 1 diabetes. Further studies are needed to compare efficacy of closed-loop with other modes of insulin delivery and assess impact on neonatal outcomes.

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1347-P

The Influence of Carbohydrate Consumption on Glycemic Control in Pregnant Women with Type 1 Diabetes

BJÖRG ÁSBJÖRNSDÓTTIR, CECELIA E. AKUESON, HELLE RONNEBY, ANE RYTTER, JENS R. ANDERSEN, PETER DAMM, ELISABETH R. MATHIESEN, *Copenhagen, Denmark*

The aim was to study the influence of carbohydrate consumption on glycemic control in pregnant women with type 1 diabetes. A retrospective study of singleton pregnancies in women with type 1 diabetes referred in early pregnancy to Rigshospitalet between Jan 2013 and Dec 2014. All women completed 1-3 days of diet recording early in pregnancy. Our experienced dietician calculated the total carbohydrate consumption/day from the major sources (e.g., bread, potatoes, rice, pasta, dairy products, candy) and estimated the glycemic index (scale 0-7). HbA1c was measured and early gestational weight gain defined as the difference between self-reported pre-pregnancy weight and weight at first pregnancy visit. In total 107 women with median HbA1c of 49 (range 32-78) mmol/mol, pre-pregnancy BMI of 24 (18-37) kg/m^2, insulin dose of 0.59 (0.25-1.35) IU/kg/24 h and early gestational weight gain of 2 (-2-8) kg were included at 62 (38-116) gestational days. The carbohydrate consumption from major sources was 182 (37-300) g/day. Daily carbohydrate consumption (r=0.279, P=0.004) and glycemic index (r=0.238, P=0.02) were positively associated with HbA1c in early pregnancy, respectively, while the day-to-day variation in carbohydrate consumption was positively associated with early gestational weight gain (r=0.27, P=0.02). The women using carbohydrate counting (45%) had a lower HbA1c at first visit (47 vs. 50 mmol/mol, P=0.03) and lower carbohydrate consumption (164 vs. 185 g/day, P=0.04) compared to those not using carbohydrate counting. Eating at least 3 snacks daily was associated with higher carbohydrate consumption compared to eating 2 snacks daily or less (193 vs. 167 g/day, P=0.01). The daily carbohydrate consumption and glycemic index were positively associated with HbA1c in early pregnancy in women with type 1 diabetes. The use of carbohydrate counting to obtain an appropriate carbohydrate intake may improve glycemic control in pregnant women with type 1 diabetes.

1348-P

Dietary Quality and Glycemic Control in Gestational Diabetes Mellitus (GDM): The Gem Study

MEGHANA D. GADGIL, SAMANTHA F. EHRLICH, MONIQUE M. HEDDERSON, SUSAN D. BROWN, ASSIAMIRA FERRARA, *San Francisco, CA, Oakland, CA*

Poor dietary quality has been associated with risk of GDM and type 2 diabetes. Its impact on glycemic control in GDM is less well characterized. This study examined the associations between dietary quality and capillary glucose control in 1,412 women with GDM. Diet during pregnancy was assessed by the Block Food Frequency Questionnaire and dietary quality was calculated by a Healthy Eating Index (HEI)-2010 score (0-100). Self-monitored capillary glucose levels were reported for 6 weeks after diet assessment. Glycemic control was defined as >80% of glucose measures below the following thresholds: fasting < 95 mg/dl and 1-hr postprandial < 140 mg/dl. Multivariable linear regression was used to calculate differences in mean glucose levels across HEI-2010 quartiles, and logistic regression was used to approximate the odds ratios and 95% CIs between HEI-2010 score and glycemic control. Decreases in 1-hr post breakfast, lunch and dinner glucose were detected with increasing quartile of HEI-2010 score. The 4th quartile of HEI-2010 score was associated with increased odds of postprandial glycemic control (Table). There was no association between dietary quality and fasting plasma glucose. Dietary quality at GDM diagnosis is associated with post-prandial glycemic control in women with GDM. Dietary quality may lower postprandial glucose, but it does not affect hepatic glucose production as reflected by fasting glucose.

Table.

Adjusted[1] Mean Difference in Glucose by Quartile of HEI 2010 Score; Mean (95% CI)[2]						Odds of Glycemic Control; OR (95% CI)	
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-trend	Quartile 4[2]	*p*-value
HEI-2010 score	43.6 (4.5)	52.1 (1.5)	57.1 (1.3)	62.4 (2.6)	<0.001	–	–
Fasting	–	-0.88 (-2.1, 0.3)	-1.2 (-2.3, -0.02)	-0.5 (-1.6, 0.6)	0.2	1.00 (0.87, 1.14)	0.98
1- h after Breakfast	–	-2.3 (-4.1, -0.6)	-2.1 (-3.9, -0.4)	-1.6 (-3.3, 0.2)	0.01	1.28 (1.10, 1.48)	0.001
1-h after Lunch	–	-1.3 (-2.9, 0.3)	-1.4 (-3.0, 0.2)	-1.3 (-2.9, 0.3)	0.03	1.12 (0.99, 1.27)	0.07
1-h after Dinner	–	-2.7 (-4.3, -1.1)	-2.7 (-4.4, -1, 1)	-2.2 (-3.8, -0.6)	<0.001	1.14 (1.01, 1.29)	0.04

[1] Adjusted for age at OGTT, race/ethnicity, physical activity (Met-minutes/week), prepregnancy BMI and randomization assignment. [2] As compared with Quartile 1.

1349-P

Adverse Neonatal Outcomes in Pregnancies Treated with Glyburide

MAISA N. FEGHALI, STEVE N. CARITIS, JANET M. CATO, CHRISTINA SCIFRES, *Pittsburgh, PA, Oklahoma City, OK*

Glyburide is the most common treatment for gestational diabetes (GDM). However, recent data has demonstrated that it crosses the placenta, and concerns about the neonatal effects of glyburide treatment including fetal overgrowth and neonatal hypoglycemia persist. We sought to examine treatment factors including total dose and duration of glyburide treatment associated with macrosomia, neonatal hypoglycemia, and neonatal composite morbidity in women treated with glyburide throughout pregnancy. Using a retrospective cohort of 721 women with GDM treated with glyburide throughout pregnancy. Maternal characteristics including blood glucose values and neonatal outcomes were collected. Bivariate and multivariable logistic regression analyses were used to assess the association between maternal and treatment characteristics and neonatal outcomes. Glyburide dosing was divided into categories of <5 (n=407), 5-9.9 (n=189), 10.-14.9 (n=79), and ≥15 mg per day (n=46). These increasing doses of glyburide were associated with an increased risk for macrosomia (5.4 vs. 12.7 vs. 10.1 vs. 13.0%, p=0.01), hypoglycemia (11.6 vs. 12.8 vs. 21.8 vs. 26.1%, p=0.009), and neonatal composite morbidity (17.2 vs. 19.7 vs. 30.8 vs. 34.8%, p=0.003). Glyburide dose ≥5 mg/day was associated with increased risk for macrosomia (aOR 2.3, p=0.01) and glyburide dose ≥10 mg/day was associated with increased risk for neonatal composite morbidity (aOR 1.9, p=0.01) and a trend towards increased neonatal hypoglycemia (aOR 1.7, p=0.07) after adjustment for covariates including age, nulliparity, pre-pregnancy BMI, weight gain, maternal glucose values, and gestational age at delivery. The duration of glyburide therapy was not associated with any adverse neonatal outcome. Our findings suggest a dose-dependent risk for adverse neonatal outcomes in women receiving glyburide, independent of glycemic control. Further studies are needed to determine optimal management of women receiving glyburide therapy, specifically women requiring higher doses.

1350-P

Metabolomic Profiling of Second Trimester Amniotic Fluid from Mothers with Diabetes during Pregnancy Shows Evidence of Altered Fetal Metabolism

JACQUELINE ALEXANDER, RIKKA AZUMA, SARA E. PINNEY, *Philadelphia, PA*

Background: Diabetic during pregnancy (DDP) induces marked abnormalities in fetal metabolism that can result in abnormal fetal growth.

Objective: To characterize the global metabolic signature of the developing fetus exposed to DDP by profiling changes in metabolomics in 2nd trimester amniotic fluid (AF).

Design/Methods: AF from 20 women with DDP and 20 healthy controls was collected at GA 16-18 weeks. Analysis of 459 metabolites was performed at Metabolon, Inc. Statistical analyses included Welsh's 2 sample and matched pairs t-tests, and FDR.

Results: Analysis reveals altered levels of 69 metabolites (28 increased, 41 decreased; p<0.05). Random Forest Plot analysis differentiates the DIP and control groups with a predictive accuracy of 73% consistent with profound metabolic profile differences. Principal component analysis shows a shift in the global metabolic profile that is more pronounced when separated by sex.

Table.

Pathway	Metabolite	Fold Change	P value	Q value
Impaired Glucose Metabolism	glucose	1.19	0.036	0.219
	2-hydroxybutyrate	1.50	0.011	0.017
	1, 5 anhydroglucitol	0.73	0.022	0.182
Gamma Glutamyl Amino Acids	gamma-glutamyl tyrosine	0.50	0.021	0.182
	gamma-glutamyl valine	0.69	0.017	0.168
Fatty Acid Metabolism: Long Chain Fatty Acids	palmitoleate (16:1n7)	3.32	0.022	0.182
	stearate (18:0)	1.19	0.013	0.165
	eicosenoate (20:1n9 or 11)	1.88	0.007	0.134
Fatty Acidy Metabolism: Polyunsaturated Fatty Acids (n3 and n6)	eicosapentaenoate (EPA; 20:5n3)	1.46	0.002	0.099
	docosahexaenoate (DHA; 22:6n3)	1.45	0.004	0.115
	linoleate (18:2n6)	1.73	0.001	0.099
	linolenate [alpha or gamma; (18:3n3 or 6)]	2.05	0.013	0.165
	dihomo-linolenate (20:3n3 or n6)	1.97	0.004	0.115
	arachidonate (20:4n6)	1.61	0.001	0.099
	docosapentaenoate (n6 DPA; 22:5n6)	1.45	0.038	0.226
	glycerol	1.23	0.025	0.187
Ketone Bodies	3-hydroxybutyrate (BHBA)	1.55	0.002	0.099
Sphingolipid Metabolism	stearoyl sphingomyelin	1.21	0.033	0.211

Conclusions: Metabolomic profiling of 2nd trimester AF from women with DIP suggests that fetal metabolism may be altered weeks before gestational diabetes is diagnosed clinically.

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1351-P

Diagnostic Thresholds for Gestational Diabetes and Programming for Childhood Overweight and Obesity

SAMANTHA F. EHRLICH, MONIQUE M. HEDDERSON, SUSAN D. BROWN, FEI XU, ASSIAMIRA FERRARA, *Knoxville, TN, Oakland, CA*

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommends lower diagnostic thresholds for GDM based on their associations with delivering a large for gestational age neonate. However, the thresholds at which the risk of childhood obesity increases remain unclear. This cohort study, among 45,872 mother-child pairs delivering at Kaiser Permanente Northern California in 1995-2004, used electronic health record data to estimate the association of fasting, 1-hour and 2-hour glucose with childhood overweight/obesity and obesity for four mutually exclusive groups: 1.) glucose below the IADPSG threshold (reference); 2.) glucose meeting the IADSGG but below the Carpenter and Coustan (CC) threshold; 3.) glucose meeting the CC but below the National Diabetes Data Group (NDDG) threshold; and 4.) glucose meeting the NDDG threshold. During this period in this setting, only women meeting the NDDG criteria received a GDM diagnosis and treatment. Childhood overweight/obesity [OR= 1.26 (95% CI 1.03, 1.55)] and obesity [1.28 (1.02, 1.60)] were only associated with meeting the NDDG threshold for fasting; similar findings were obtained when women with GDM by the full NDDG criteria (i.e., the treated) were excluded. Results suggest that programming for childhood overweight/obesity and obesity only occurs with pregnancy fasting glucose ≥105 mg/dl, as previously recommended by the NDDG.

Table.

	OR [a] (95% CI) for Childhood Overweight/ Obesity at 5-7 years of age	OR [a] (95% CI) for Childhood Obesity at 5-7 years of age
Fasting glucose		
Below IADPSG threshold	1.00	1.00
IADPSG (95 mg/dl > fasting ≥ 92 mg/dl)	1.02 (0.83, 1.24)	1.04 (0.82, 1.31)
CC (105 mg/dl > fasting ≥ 95 mg/dl)	1.08 (0.94, 1.26)	1.10 (0.93, 1.31)
NDDG (fasting ≥ 105 mg/dl)	**1.26 (1.03, 1.55)**	**1.28 (1.02, 1.60)**
1-hour glucose		
Below IADPSG threshold	1.00	1.00
CC/IADPSG* (190 mg/dl > 1-hour ≥ 180 mg/dl)	0.97 (0.83, 1.13)	1.08 (0.90, 1.29)
NDDG (1-hour ≥ 190 mg/dl)	1.10 (1.00, 1.21)	1.09 (0.97, 1.22)
2-hour glucose		
Below IADPSG threshold	1.00	1.00
IADPSG (155 mg/dl > 2-hour ≥ 153 mg/dl)	0.81 (0.57, 1.17)	0.94 (0.61, 1.46)
CC (165 mg/dl > 2-hour ≥ 155 mg/dl)	1.05 (0.91, 1.22)	1.07 (0.90, 1.28)
NDDG (2-hour ≥ 165 mg/dl)	1.05 (0.95, 1.15)	1.10 (0.98, 1.23)

* Both CC and IADPSG criteria have 1-hour threshold of 180 mg/dl.
[a] Adjusted for maternal age, race-ethnicity, parity, education, pregnancy BMI, and gestational age at the pregnancy BMI measurement.

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1352-P

Combined Liraglutide + Metformin Is Superior to Metformin Monotherapy in Reducing Body Weight and Improving Metabolic Parameters in Overweight Women with Prior Gestational Diabetes

KAREN ELKIND-HIRSCH, MARTHA PATERSON, DONNA SHALER, HANH GUTOWSKI, *Baton Rouge, LA*

Gestational diabetes (GDM) is a major risk factor for diabetes. Postpartum weight gain is strongly associated with deterioration of glycemic control in prior GDM women. Liraglutide, a GLP-1 agonist, has been shown to be more effective in reducing body weight compared with Metformin. This study evaluated liraglutide + Metformin (MET-LIRA) vs. placebo + Metformin (MET-P) therapy in overweight women with recent GDM.

Overweight women (n=95; BMI > 25; 18 -45 y; GDM within 12 months) with postpartum metabolic abnormalities were randomized to MET-LIRA (MET, 2000mg, LIRA 1.8 mg SC QD) or MET-P (MET, 2000mg, placebo SC QD) for 36 weeks. BMI and waist size (WC) were measured at each visit. A 75g OGTT was done at baseline and follow-up to assess glycemia, fasting (FBG) and mean blood glucose (MBG) and compute insulin sensitivity (IS) and secretion (SI) measures. Lipids were measured in the fasting sample.

Sixty-five women (68%) completed follow-up; 34/47 MET-LIRA and 31/48 MET-P. Both therapies improved BMI, WC, IGI/HOMA but MET-LIRA was more effective in reducing BMI. MET -LIRA therapy but not MET P decreased TRG/HDL ratio and MBG, and increased IS_{OGTT*} and IS-SI (Table 1).

Table 1.

	MET-LIRA		MET-P		P-value
Parameter	Baseline	Post-Treatment	Baseline	Post-Treatment	Main, Interaction
BMI (kg/m2)	37+/-1.3	35+/-1.3	34+/-1.3	33.6+/-1.4	0.001[a]; 0.018[b]
WC (cm)	99.1+/-2.2	96.5+/-2.3	96.5+/-2.4	94+/-2.5	0.001[a]
TRG/HDL ratio	3.1+/-.3	2.7+/-.25	3.0+/-.3	3.3+/-.26	NS, p <0.03[b]
FBG (mg %)	97+/-1.7	94+/-1.5	92.4+/-1.8	92+/-1.6	NS
MBG (mg %)	135+/-4	130+/-4	123+/-4	128+/-4	NS, P <0.03[b]
HOMA	2.9+/-.23	2.5+/-.3	2.6+/-.24	2.8+/-.32	NS
IS_{OGTT**}	3.7+/-.4	4.6+/-.4	5+/-.4	4.8+/-.45	NS, p <0.03[b]
IGI/HOMA	0.48+/0.5	0.6+/-0.65	0.51+/-0.54	0.52+/-0.68	0.05[a]
IS-SI	242+/27	292+/-29	271+/-29	252+/-31	NS, p <0.035[b]

BMI=body mass index; WC=waist circumference; TRG/HDL=triglyceride to HDL-cholesterol; IGI/HOMA=insulinogenic index adjusted for insulin sensitivity; IS-SI=oral disposition index. Values are presented as mean +/- SEM.
[a] Main drug treatment effect. [b] MET -LIRA vs. MET-P.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

The addition of liraglutide to Metformin provided greater reduction in BMI and also improved insulin action and lipid profiles compared to Metformin alone.

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1353-P

Breastfeeding Status at Hospital Discharge Predicts Long-Term Breastfeeding Intensity after GDM Pregnancy

REENA OZA-FRANK, RASHMI KACHORIA, *Columbus, OH*

Breastfeeding intensity, proportion of feedings that are breast milk, is inversely associated with type 2 diabetes risk after GDM pregnancy. Although women with GDM are more likely to experience reduced breastfeeding intensity during hospital stay due to medical recommendation for formula supplementation, they still have the opportunity to increase breastfeeding intensity by hospital discharge and beyond. However, the association between breastfeeding status at hospital discharge and long-term breastfeeding intensity by GDM status remains unknown. We used data from the 2005-2007 Infant Feeding Practices Study II (n=1957). Women completed monthly questionnaires on infant feeding through 12 months. We used linear regression to determine the associations between GDM, breastfeeding status at discharge (exclusive or not), and breastfeeding intensity adjusted for maternal race, age, insurance, WIC, marital status, mother's education, gestational age, parity, prepregnancy weight, and delivery method. Overall, breastfeeding intensity among women with GDM (6.4%) was lower at 3 months compared with women without diabetes (54% vs. 65%; p=.02). Regardless of GDM status, women who exclusively breastfed at hospital discharge continued to breastfeed with more intensity at 3 months (69% vs. 75%; p=.3) than women who did not exclusively breastfeed at hospital discharge (30% vs. 30%; p=.9). In adjusted models, GDM status was not associated with intensity whereas breastfeeding status at discharge was (beta coefficient=44.6; p=<.01). Similar trends for breastfeeding intensity were observed at 6 months. Breastfeeding status at hospital discharge was an important factor in predicting breastfeeding intensity at 3 and 6 months, regardless of GDM status. Additional support may be necessary to maximize breastfeeding intensity by discharge and beyond among women with GDM who are at risk for lower breastfeeding intensity during hospital stay.

1354-P

Sleep and Napping during the 1st and 2nd Trimester of Pregnancy and Subsequent Risk of Gestational Diabetes

SHRISTI RAWAL, STEFANIE N. HINKLE, YEYI ZHU, PAUL ALBERT, CUILIN ZHANG, *Rockville, MD*

Both short and prolonged nighttime sleep duration have been linked to type 2 diabetes due to their adverse impact on insulin sensitivity. Sleep difficulty is common in pregnancy, but prospective data is limited on its relation to gestational diabetes (GDM). In the NICHD Fetal Growth Study (n=2584), a prospective, multiracial cohort of healthy women without diabetes before pregnancy, we examined the relation of sleep duration and napping frequency to GDM risk. GDM (n=107) was diagnosed by medical record review. In the 1st (8-13 gestational weeks) and 2nd (16-22 weeks) trimesters, women reported their typical sleep duration (5-6, 7, 8-9 or 10+ hours) and napping frequency (most times, sometimes or rarely/never) in the preceding week. Adjusted relative risks (aRRs) [95% confidence interval (CI)] for GDM were estimated with Poisson regression, adjusting for demographics, prepregnancy body mass index, and other risk factors. From the 1st to 2nd trimester, women were less likely to sleep for 10+ hours (24.4% vs. 14.7%) or to nap some/most times (80.4% vs. 54.4%). Sleeping duration and napping in the 1st trimester were not independently or jointly related to GDM risk. However, significant relations were observed in the 2nd trimester. Compared to women who slept for 8-9 hours and did not nap (rarely/never), aRRs (95% CI) were 2.65 (1.32-5.33) for women who slept less (5-7 hours) and did not nap, 2.07 (1.07-4.02) for those who slept 8-9 hours and napped (some/most times), and 2.24 (1.02-4.92) for those who slept more (10+ hours) and napped. In addition, the relation of 2nd trimester sleep and GDM differed by obesity status (p for interaction=0.04). Only among nonobese women, sleeping more or less than 8-9 hours were both significantly related to GDM risk; aRRs (95% CI) were 2.53 (1.28-4.99) for 5-6 hours, 1.98 (1.08-3.64) for 7 hours, and 2.37 (1.15-4.88) for 10+ hours. Our data suggest a U-shaped relation between sleep duration and GDM and that napping and obesity status may modify this relation.

1355-P

Clinical Outcomes in Obese Women with Weight Loss after the Diagnosis of Gestational Diabetes

CHRISTINA SCIFRES, MAISA FEGHALI, STEVE N. CARITIS, JANET CATOV, *Oklahoma City, OK, Pittsburgh, PA*

Women diagnosed with gestational diabetes mellitus (GDM) undergo dietary counseling, and this frequently alters their weight gain trajectory. However, clinical outcomes associated with weight loss after a diagnosis of GDM in obese women are not well understood. We therefore perfomed a retrospective cohort study of 641 obese women with GDM. Maternal characteristics including glucose values and neonatal outcomes were abstracted. Bivariate and multivariable logistic regression analyses were used to assess the association between maternal characteristics and neonatal outcomes. Of the obese women with GDM, 151 (24.6%) had either no weight gain or weight loss after their GDM diagnosis. Women without weight gain had similar glucose testing results and weight gain prior to diagnosis, but less weight gain after diagnosis (-4.1 vs. 10.1 lbs, p<0.001) compared with women who gained weight. Mean fasting glucose was similar between women in the no weight gain and weight gain groups, but the former had lower mean post-prandial glucose (123.1 vs. 126.8 mg/dL, p=0.02). No weight gain was associated with similar rates of macrosomia and large or small for gestational age birth weight. However, women without weight gain had lower mean birth weight (-123 g, 95% CI -217 to -30 g, p=0.01) after adjustment for age, nulliparity, pre-pregnancy BMI, weight gain before diagnosis, glucose values, tobacco use, and gestational age at delivery. No weight gain was also associated with a decreased risk for cesarean delivery (OR 0.61, 95% CI 0.39-0.96, p=0.03) after adjustment for pre-pregnancy BMI, weight gain prior to diagnosis, age, glucose values, and nulliparity. There were no differences in risk for hypertensive disorders of pregnancy, neonatal intensive care admission, or neonatal morbidity between groups. These results suggest that weight loss after GDM diagnosis may have benefits with regards to glycemic control and risk for cesarean delivery without significantly increasing the risk for fetal growth restriction.

1356-P

Breastfeeding at One Week Is a Better Predictor of Breastfeeding Duration than Gestational Diabetes Status

REENA OZA-FRANK, RASHMI KACHORIA, *Columbus, OH*

Longer duration of breastfeeding is associated with lower incidence of type 2 diabetes after gestational diabetes mellitus (GDM) pregnancy. Previous data indicates women with GDM have shorter breastfeeding durations than women without diabetes. However there is no literature examining differences in breastfeeding duration by GDM status among women who successfully breastfed for the first week, a factor positively associated with breastfeeding duration. Data are from the Pregnancy Risk Assessment Monitoring System (2009-2011) from 30 states and New York City. Women who were still breastfeeding at 1 week were included in the analysis; women with pregestational diabetes were excluded. Chi-square tests were used to test differences in breastfeeding duration by GDM. Multivariable linear regression was used to examine the association between GDM and weeks breastfeeding. Among (N=65,600, 8.6% GDM) women still breastfeeding at 1 week, fewer women with GDM exclusively breastfed in the first week compared with women without diabetes (51% vs. 63%, p=<.01). Regardless of this, women with GDM went on to breastfeed for longer than with women without diabetes (11 vs. 10 weeks, p=<.01). In adjusted models, GDM was significantly associated with an increase in breastfeeding duration (beta=.46; p=.04). If women were exclusively breastfeeding at 1 week, there was no difference in breastfeeding duration by diabetes status (GDM: 13 vs. no diabetes: 13 weeks, p=.8). In adjusted models, similarly, there was no significant difference by diabetes status (beta=-.03; p=.9). Despite the convention that introducing liquids other than breast milk early results in reduced breastfeeding duration, our results indicate that any breastfeeding through the first week of life results in similar breastfeeding duration regardless of GDM status. This reinforces the need for encouraging early breastfeeding to maximize breastfeeding duration after GDM pregnancy.

1357-P

Baseline Characteristics and Cardiovascular Outcomes in Women with a History of Gestational Diabetes in the Evaluation of LIXisenatide in Acute Coronary Syndrome Trial

RHONDA BENTLEY-LEWIS, BRIAN CLAGGETT, JIANKANG LIU, ALDO P. MAGGIONI, JOHN J.V. MCMURRAY, JEAN-CLAUDE TARDIF, LARS V. KØBER, SCOTT D. SOLOMON, ELDRIN F. LEWIS, *Boston, MA, Florence, Italy, Glasgow, United Kingdom, Montreal, QC, Canada, Copenhagen, Denmark*

Gestational diabetes mellitus (GDM) has been increasing in prevalence and its influence on cardiovascular (CV) disease risk has been increasingly recognized. We aimed to examine the baseline characteristics and CV outcomes of women with and without a history of GDM.

The Evaluation of LIXisenatide in Acute Coronary Syndrome (ELIXA) trial was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of lixisenatide in patients with type 2 diabetes and recent acute coronary syndrome (ACS). Women enrolled provided details regarding GDM history and insulin use during pregnancy. We then compared women with and without a history of GDM according to baseline clinical characteristics; CV and diabetes medications; lifestyle data; patient-reported outcome data obtained from the Diabetes Health Profile (DHP-18); and subsequent CV outcomes.

Among the 1861 women enrolled in ELIXA, women with a history of GDM (n=51) compared to women without a GDM history (n=1810) were significantly younger (54 ± 11 vs. 63 ± 9 yrs; p < 0.001); had an earlier age at diabetes diagnosis (36 ± 9 vs. 52 ± 11 yrs; p < 0.001); and had a higher HbA1c (median [IQR], 8.2 [7.2, 9.2] vs. 7.6 [6.7, 8.7]%; p = 0.035). Women with a history of GDM had more percutaneous coronary interventions (76.5 vs. 56.8%; p = 0.005); more coronary artery bypass grafts (13.7 vs. 6.0%; p = 0.025); and less mobility-difficulty reported compared to women without a GDM history (21.1 vs. 46.9%; p = 0.027). During a median follow-up of 25 months, the all-cause death, CV death, myocardial infarction, heart failure, and stroke event rates were statistically similar between women with and without GDM.

Among women with type 2 diabetes and recent ACS, women with a GDM history were younger at age of diabetes onset and had more CV revascularizations than women without a GDM history. Further examination of GDM and CV outcomes is warranted. (NCT01147250).

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1358-P

The Association between Lipid Measures at Mid-pregnancy and Postpartum Glucose Metabolism in Women with Gestational Diabetes Mellitus

KYUNG-SOO KIM, MIN-JUNG SHIM, SOO-KYUNG KIM, SEOK WON PARK, YONG-WOOK CHO, *Seongnam, Republic of Korea*

The aim of this study was to evaluate the association between lipid measures at mid-pregnancy and the status of postpartum glucose metabolism at 6-12 weeks after delivery in women with gestational diabetes mellitus (GDM). We enrolled 626 pregnant women diagnosed with GDM from October 2005 to December 2013. Lipid profiles were measured during 24-32 gestational weeks and 75-g OGTT was performed at 6-12 weeks after delivery. Postpartum glucose intolerance was defined as fasting plasma glucose (FPG) ≥ 100 mg/dL or 2-h plasma glucose (2-h PG) ≥ 140 mg/dL. Mean age was 32.9 ± 3.6 years and mean pre-pregnancy BMI was 22.5 ± 3.6 kg/m^2. The prevalence of postpartum glucose intolerance was 53.5% (n = 335). Although total cholesterol (TC) and HDL-cholesterol (HDL-C) levels were not significantly different between two groups, women with postpartum glucose intolerance had higher triglyceride (TG) level and TG to HDL-C (TG/HDL-C) ratio at mid-pregnancy than those with normal glucose tolerance (P< 0.05). TG level and TG/HDL-C ratio were positively correlated with FPG, 2-h PG and insulin resistance as calculated by homeostatic model assessment (HOMA-IR) at postpartum 6-12 weeks but TC and HDL-C levels were not. After adjustment for maternal age and pre-pregnancy BMI, TG level and TG/HDL-C ratio still correlated with FPG (r = 0.23, P< 0.001; r = 0.23, P< 0.001) and HOMA-IR (r = 0.16, P< 0.001; r = 0.15, P< 0.001), respectively. TG level and TG/HDL-C ratio were independently and significantly associated with the prevalence odds of postpartum glucose intolerance (OR 1.00 [95% CI 1.00-1.01], OR 1.12 [95% CI 1.01-1.24)] after adjustment for maternal age, pre-pregnancy BMI, and FPG. Among lipid meaures, TG and TG/HDL-C ratio can be good markers to predict the risk of postpartum glucose intolerance in women with GDM.

1359-P

Differences in Adiponectin and Leptin in Adolescent Offspring of Women with Type 1 Diabetes: Results from the EPICOM Study

ZUZANA VLACHOVÁ, BIRGITTE BYTOFT, SINE KNORR, TINE D. CLAUSEN, RIKKE BECK JENSEN, HENNING BECK-NIELSEN, PETER OTURAI, ANNE PERNILLE HERMANN, JAN FRYSTYK, CLAUS H. GRAVHOLT, PETER DAMM, KURT HØJLUND, DORTE MØLLER JENSEN, *Odense, Denmark, Copenhagen, Denmark, Aarhus, Denmark, Hillerød, Denmark*

In the EPICOM (EPIgenetic, genetic and environmental effects on growth, COgnitive functions and Metabolism in offspring of women with type 1 diabetes) Study we have previously demonstrated less favourable metabolic profile in offspring born to women with type 1 diabetes (T1DM) compared with offspring from the background population. Adiponectin and leptin are thought to play important roles in the regulation of metabolic and cardiovascular homeostasis. In this part of the EPICOM study we aimed to investigate: 1.) Adiponectin and leptin levels in adolescents exposed to maternal T1DM compared with non-exposed adolescents from the background population, 2.) Associations between adiponectin and leptin in adolescence and maternal glycemic control during pregnancy. We measured serum levels of adiponectin and leptin in 271 offspring of women with T1DM in pregnancy (index offspring) (13-20 years) and 297 matched control offspring. Anthropometric measurements including dual-energy X-ray absorptiometry scans to assess total body fat (TBF) and oral glucose tolerance tests were performed. We found that adiponectin levels were lower in index females: -8.0% (95% CI; -13.9, -1.6), but not in index males: 0.4% (95% CI; -7.3, 8.6). Leptin levels were approximately 30% higher in index than control offspring both females: 32.1% (95% CI; 13.5, 53.6) and males: 32.7% (95% CI; 6.1, 65.9). In males, this was seen despite similar TBF in index and control offspring. Male offspring had significantly lower leptin levels (more than six-fold) than female offspring regardless the index/control status. We observed no direct associations between the maternal HbAc levels in pregnancy and adiponectin and leptin levels in the offspring. In conclusion, abnormal levels of adiponectin and leptin were present in adolescent offspring of women with T1DM, especially in females, but no direct association between maternal glycemic control and adiponectin and leptin levels in the offspring was found.

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1360-P

The Influence of Carbohydrate and Fat Consumption in Pregnant Women with Type 1 Diabetes on Maternal Blood Glucose and Fetal Weight

KIRSTEN L. THOMAS, ROSEMARY B. CATANZARO, JEFFREY A. GAVARD, KATHRIN A. ELIOT, RABIA S. RAHMAN, DOROTHEA J. MOSTELLO, *St. Louis, MO*

Maternal glucose levels are known to contribute to birth weight. We examined how the macronutrient intake of carbohydrate and fat in pregnant women with type 1 diabetes (T1DM) relates to delivery of a large-for-gestational age (LGA) infant. Food and glucose records from 50 women with T1DM during weeks 29-32 of pregnancy were assessed. Maternal glycemic indicators and carbohydrate and fat intake at meals and snacks were compared between those delivering LGA vs. non-LGA infants. Women delivering LGA infants consumed higher percentages of high-fat meals (31.3 ± 15.3 vs. 21.7 ± 17.2, p<0.05) and high-fat meals plus snacks (28.7 ± 15.3 vs. 18.2 ± 15.1, p<0.05) compared to women delivering non-LGA infants. Mean carbohydrate content of meals and snacks, total daily carbohydrate, and proportions of meals with moderate (≥45-75 g), high (≥75-100g), and very high (≥100g) amounts of carbohydrate did not differ significantly between groups. Fasting blood glucose percentage above target of 90 mg/dl (p<0.05), cesarean delivery (p<0.01), and prior delivery of LGA infant (p=0.05) also were significantly associated with an LGA infant. Maternal weight gain (18.7 ± 6.8 vs. 13.9± 5.4 kg, p<0.01) and rate of gain (0.5 ± 0.2 vs. 0.4 ± 0.1 kg/wk, p<0.05) were higher in women delivering LGA infants. Maternal weight gain per kg [adjusted odds ratio [(aOR) 1.136, 95% confidence interval (CI) 1.023-1.262, p<0.05] and percentage of high fat meals and snacks per % (aOR 1.049, 95% CI 1.004-1.096, p<0.05) were final independent predictors of an LGA infant in a multiple logistic regression model. Percentage of high-fat meals and snacks demonstrated good discriminatory ability between women delivering LGA infants and non-LGA infants through receiver operating characteristic (ROC) curve analysis (p<0.05) with an optimal cutoff of 21%. In pregnant women with T1DM, a high-fat diet and maternal weight gain are associated with an LGA infant and are potentially modifiable risk factors.

For author disclosure information, see page A696.

Moderated Poster Discussion ADA-Supported Research

1361-P

Perinatal Risk Associated with Accelerated Fetal Growth and Polyhydramnios with a Normal Gestational Diabetes Mellitus (GDM) Screen

CECILIA MO, SARAH CRIMMINS, CHRIS HARMAN, OZHAN TURAN, *Washington, DC, Baltimore, MD*

Fetal macrosomia and associated perinatal complications are seen with uncontrolled diabetes mellitus (DM) but also in pregnancies without DM. We investigated perinatal outcome in fetuses with ultrasonographic evidence of maternal insulin resistance (accelerated growth and/or polyhydramnios) with normal DM screening to determine if maternal and neonatal complications were similar to DM.

Retrospective study. Singleton, non-anomalous pregnancies who had a normal DM screen with polyhydramnios (AFI >24cm/MVP >8cm) and/or accelerated fetal growth (AC >95th percentile) were recorded as ultrasound indicated cases (UIC). Maternal demographics, delivery outcome (gestational age [GA] at delivery, delivery mode, shoulder dystocia (SD), lacerations, placental weight [PIW], estimated blood loss [EBL], and APGAR scores), and neonatal data (birth weight percentile [BW%], NICU admission, sepsis, hypoglycemia, respiratory distress, intubation>6h, glucose, IV dextrose use, stillbirth, neonatal death and length of stay) were noted. Composite morbidity (CM) was tabulated. UIC were compared to control (normal DM screening, no polyhydramnios or accelerated fetal growth), GDM, and pregestational DM (pGDM) pregnancies.

383 cases met study criteria. BMI in UIC was higher than control but lower than GDM and pGDM ($p<0.005$ for all). BW%, EBL, PIW, SD and CM were higher in UIC than control ($p<0.01$ for all). Neonatal hypoglycemia did not attain significance in UIC vs. control ($p=0.053$). BW%, EBL, risk of hypoglycemia and CM were lower in UIC than in GDM and pGDM ($p<0.01$). SD and lacerations were similar ($p>0.05$) between UIC and GDM and pGDM. Subanalysis of entry criterion (individual ultrasound markers) did not alter the risk of delivery or neonatal outcomes ($p>0.05$).

Pregnancies with polyhydramnios and/or accelerated fetal growth with normal DM screen are at higher risk for maternal and neonatal complications, comparable to diabetic pregnancies.

Supported By: National Institutes of Health

1362-P

The Association between Vascular Complications of Type 1 Diabetes Mellitus during Pregnancy and Congenital Malformations

LEYLA SAMII, MELISSA KALLAS-KOEMAN, LOIS DONAVAN, ABHAY LODHA, SUSAN CRAWFORD, SONIA BUTALIA, *Calgary, AB, Canada*

Studies have inconsistent findings on the association of diabetes related vascular disease and congenital anomalies. To aid clinicians in effective patient counseling, our objective was to assess this relationship in women with type 1 diabetes.

We assessed the association between vascular complications (retinopathy, nephropathy and pre-existing hypertension) and congenital malformations in 232 mothers with type 1 diabetes who presented to 3 specialty clinics from 2006 to 2010.

Average maternal age (31.8 ± 5.0 vs. 29.4 ± 4.7 years, $p<0.01$), diabetes duration (20.9 ± 6.7 vs. 11.2 ± 7.4 years, $p<0.01$) and preeclampsia rate (12.5% vs. 1.3%, $p<0.01$) were higher in mothers with vascular complications compared to those without. There was no significant difference between the two groups in preterm delivery (41% vs. 30.6%, $p=0.2$) and small for gestational age newborn rate (2.6% vs. 1.9%, $p=0.75$). Congenital anomalies were not associated with hypertension or retinopathy. There was a trend for nephropathy to be associated with increased rate of major anomalies, though it was not significant (25% vs. 8.8%, $p=0.07$). Pregnancies with major congenital malformations, had higher pre-conception ($p<0.01$) and trimester specific A1c ($p<0.05$). Multivariate analyses, including maternal age, diabetes duration, smoking, preconception care, A1c and vascular complications, showed that the average A1c was sole predictor of major congenital anomalies (OR=2.25, 95% CI: 1.3-3.9) and that there was no increased risk with vascular complications (OR=1.90, 95% CI: 0.5-7.1).

Our study showed that pre-existing vascular complications were not associated with an increased risk of congenital malformations in mothers with type 1 diabetes. Clinicians should emphasize optimal glycemic control as a definite key intervention to prevent major congenital malformations.

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1363-P

Prepregnancy White Rice and Brown Rice Consumption in Relation to Risk of Gestational Diabetes: A Prospective Cohort Study

WEI BAO, YEYI ZHU, DEIRDRE K. TOBIAS, JORGE E. CHAVARRO, QI SUN, SHRISTI RAWAL, STEFANIE N. HINKLE, LINDA G. SNETSELAAR, FRANK B. HU, CUILIN ZHANG, *Iowa City, IA, Rockville, MD, Boston, MA*

White rice, a refined grain product of brown rice, is primarily composed of rapidly absorbable starch with a high glycemic index. Thus, high consumption of white rice may have detrimental effects on glucose metabolism. We aimed to prospectively examine the associations of pre-pregnancy white rice and brown rice consumption with risk of gestational diabetes (GDM). We included 15262 women who were free of prior GDM or pre-pregnancy chronic diseases in the Nurses' Health Study II (1991-2001). Dietary intakes were assessed every four years since 1991 via validated food frequency questionnaire. Incident GDM was ascertained based on self-report of a physician diagnosis of GDM, which was validated by medical records. We estimated relative risks (RRs) and 95% confidence intervals (CIs) using log-binomial models with generalized estimating equations. During 10 years of follow-up, we documented 839 incident GDM cases among 21258 singleton pregnancies. After adjustment for age, race, parity, dietary and non-dietary factors including BMI, the RRs (95% CIs) of GDM for white rice consumption of 1-3 servings/month, 1 serving/week, 2-4 servings/week, and ≥ 5 servings/week, compared with < 1 serving/month, were 1.08 (0.88-1.34), 1.24 (1.00-1.55), 1.18 (0.92-1.52), and 1.33 (0.83-2.15), respectively (P for trend = 0.03). The adjusted RRs (95% CIs) of GDM for brown rice consumption of 1-3 servings/month, 1 serving/week, and ≥ 2 servings/week, compared with < 1 serving/month, were 0.91 (0.78-1.06), 0.97 (0.78-1.22), and 0.90 (0.65-1.25), respectively (P for trend = 0.70). The adjusted RRs (95% CIs) of GDM associated with substituting one serving/week of white rice with brown rice or whole grain foods were 0.95 (0.84-1.06) and 0.96 (0.93-1.00), respectively. In conclusion, pre-pregnancy consumption of white rice, but not brown rice, is positively associated with the risk of GDM. Substitution of white rice with whole grain foods for GDM risk warrants further investigation.

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1364-P

Fetal Sex Is Not Associated with Gestational Diabetes Mellitus or with Placenta Weight: A Cohort Study

EMMANUEL COSSON, ABDOURAHMANE DIALLO, MIHAELA DOCAN, DORIAN SANDRE-BANON, ISABELA BANU, CAMILLE CUSSAC-PILLEGAND, SABRINA CHIHEB, PAUL VALENSI, LIONEL CARBILLON, *Bondy, France, Paris, France*

A recent systematic meta-analysis has shown an increased risk of gestational diabetes mellitus (GDM) in women carrying a male fetus compared with women carrying a female fetus. An heterogeneity in placental weight according to the presence of GDM and fetal sex would suggest that placenta may be partly involved, as placental weight is a measure commonly used to summarize placental growth and a determinant of fetal growth. Our aims were to check the association, controlling for risk factors of GDM, and to investigate the role of placenta. We included the 20,149 women without pregestational diabetes who delivered of singletons in our University hospital between January 2002 and December 2010. GDM had been universally screened and placenta weighed at delivery. GDM (14.2% of women) was not associated with fetal sex (proportion of male fetus in women without or with GDM: 51.8% vs. 51.7%, $p=0.957$), and similarly after logistic regression analysis considering the risk factors for GDM in univariate analyses (odds ratio 1.007 [95% confidence interval 0.930-1.091], $p=0.858$), i.e., age 35 years or greater, overweight, familial history of diabetes, personal history of GDM or macrosomic infant, multiparity, smoking before pregnancy, personal history of miscarriage and of hypertension, and ethnicity. Placental weight was 600±126, 596±123, 584±118 and 587±181g in women with GDM/female, GDM/male, no GDM/female and no GDM/male fetus groups, respectively (GDM effect: $p=0.015$; sex effect: $p=0.09$ and GDM*sex effect: $p=0.16$). To conclude, our results suggest that fetal sex is not associated with GDM. Placental growth might not be involved in such an association, if any.

1365-P

A Longitudinal Study of Plasma Levels of Adipokines and Gestational Diabetes: Findings from a Prospective Multiracial Cohort

CUILIN ZHANG, WILLIAM GROBMAN, STEFANIE HINKLE, YEYI ZHU, WEI BAO, MICHAEL TSAI, MARY HEDIGER, PAUL ALBERT, *Rockville, MD, Chicago, IL, Bethesda, MD, Iowa City, IA, Minneapolis, MN*

Longitudinal data on adipokines in pregnancy are sparse and their role in the etiology of gestational diabetes (GDM) remains to be elucidated. We aimed to address this knowledge gap in a case-control study of 107 women

with GDM and 214 women without GDM nested in a multiracial prospective cohort, the NICHD Fetal Growth Study, with blood samples being collected 4 times in pregnancy since gestational week (GW) 8. GDM diagnosis was made by medical record review. A comprehensive adipokine profile including chemerin, leptin, IL-6, total and high molecular weight (HMW) adiponectin, leptin receptor, vaspin, and omentin-1 was measured using plasma collected at GW 8-13, 16-22, 24-29, and 34-37. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association of GDM with adipokines in the 1st (GW 8-13) and 2nd trimester (GW 16-22) (before the GDM diagnosis) were estimated using conditional logistic regression after adjusting for age, pre-pregnancy BMI, and other risk factors of GDM. In both the 1st and 2nd trimesters, mean chemerin, leptin, and IL-6 levels were higher in women who later developed GDM than in non-GDM (all P for test of difference <0.01) and were significantly and positively related to GDM risk. For instance, in the 1st trimester, aOR (95% CI) of GDM comparing the highest vs. lowest quartile is 3.34 (1.10, 10.1) for chemerin, 10.0 (2.58, 39.0) for IL-6, and 2.77 (0.99, 7.72) for leptin. On the other hand, mean adiponectin, HMW adiponectin and leptin receptor levels in both trimesters were significantly lower in GDM women than controls. Vaspin levels were significantly related to GDM only in the 2nd trimester, (aOR (95% CI) comparing the highest vs. lowest quartile was 3.20 (1.24, 8.28)). Levels of omentin-1 in either trimester were not related to GDM risk. In conclusion, plasma levels of adipokines including several novel ones, as early as the 1st trimester, may be used to predict the occurrence of as well as give insight into the pathogenesis of GDM.

1366-P

Which Factors May Affect Pregnancy Outcomes in In Vitro Fertilization Pregnancies Complicated by Gestational Diabetes Mellitus?

PETROS THOMAKOS, OLGA KEPAPTSOGLOU, IBRAHIM TARAOUNE, CAROL BARETTO, ASTERIS KORANTZIS, DIMITRIOS TROUVAS, ANASTASIOS PANTOS, MINAS MASTROMINAS, KONSTANTINOS PANTOS, CHRISTOS ZOUPAS, *Athens, Greece*

In Vitro Fertilization (IVF) is a popular method of assisted reproduction. IVF is associated with an increased risk of gestational diabetes mellitus (GDM). In literature, there is limited information regarding the impact of GDM on IVF pregnancies. The aim of our study was to investigate the clinical characteristics of IVF pregnancies complicated by GDM and which factors may affect maternal and fetal outcomes. A cross-section study was conducted in 102 singleton IVF pregnancies affected by GDM. [(M±SD) age: 38.1±4.8 years, BMI: 23.9±5.8 kg/m^2, HbA1c: 5.3±0.7%, Fasting Blood Glucose (FBG): 85.0±9 mg/dl, 1-hour postprandial BG: 105±12 mg/dl, maternal weight gain: 10.5±8 kg, week of diagnosis GDM: 21.4±8.1, week of starting insulin 21.6±8.5, insulin dose 51.1±28.4 iu/day, week of delivery 36.9±2.1, neonatal birth weight 3062.2±493 gr, women experienced hypoglycemia episodes: 30%, miscarriage history: 35.4%, smoking history: 32.2%]. The results of obstetric- neonatal history are summarized as follows: Preeclampsia rate 5%, Respiratory Distress Syndrome 12%, Neonatal hypoglycemia 8%, Jaundice 18%, Neonatal Intensive Care Unit admittance 13.8%, Preterm birth 11%, Caesarean Section (CS) 86%. There were 2 cases of perinatal mortality and no congenital malformations. Associations between clinical characteristics and the above adverse outcomes were tested. CS was not included in the analysis. 1-hour Postprandial BG but not FBG or HbA1c, was associated with maternal-fetal complications (r=0.504, p<0.001). Insulin dosage was associated with higher rate of hypoglycemia (r=0.513, p=0.001) but hypoglycemia did not affect fetal outcome. BMI was not correlated with the week of GDM diagnosis. The data highlight that screening for GDM in IVF pregnancies should be considered much earlier than 24-28 weeks suggested by ADA. They also emphasize on the importance of strict postprandial metabolic control which can be reached with intense early insulin therapy.

1367-P

Families Defeating Diabetes (FDD): Hemoglobin A1c Testing at 3 and 12 Months

KRISTEN BARTON, LOIS DONOVAN, ISABELLE GIROUX, DAVID MILLER, MICHELLE MOTTOLA, PATRICIA ROSAS-ARELLANO, RUTH M. MCMANUS, *Calgary, AB, Canada, Ottawa, ON, Canada, Victoria, BC, Canada, London, ON, Canada*

FDD was a 12 month Canadian diabetes (DM) prevention intervention for women with recent GDM within their family context. We report 3 and 12 month results and correlations with hemoglobin A1c (HbA1c).

Women with recent GDM were randomized into two groups: intervention (I; N=89) or control (C; N=81). I women received a DM prevention seminar, ongoing information and behavioral change support for healthy diet, exercise, weight goals via website access, electronic updates 2X/month, access to weekly walking group. C women received Canadian Diabetes Association DM prevention information. Body habitus was assessed at 0, 3, 6 and 12 months, and HbA1c was measured at 3 and 12 months.

A1c results for I and C were compared at 3 and 12 months; ADA guideline tertiles of A1c results (<5.7%; 5.7-6.4%; >6.4%) were calculated and correlated with body habitus and demographics. SAS was used to calculate unpaired t-tests; Fisher's Exact test for comparison of groups for numerical results and ADA tertile results; Pearson correlations for HbA1c levels at 3 and 12 months. Significance was identified as p<0.05.

Table.

HbA1c	Interventional (N=46)	Control (N=40)	P value
3 months	0.055	0.054	NS
12 months	0.055	0.055	NS
<5.7%	30	28	NS
5.7-6.4%	16	10	NS
>6.4%	0	2	NS
Correlations between 3 and 12 month A1c			
Intervention		*r*=0.59	<0.001
Control		*r*=0.82	<0.001
Intervention + Control		*r*=0.74	<0.001

In the I group, weight loss at 12 months was associated with lower HbA1c (p=0.039).

A1c and A1c tertiles did not differ between I and C women who completed 12 months of the FDD study. However, A1c results at 3 and 12 months were strongly correlated for study and combined groups, a finding with potential clinical relevance to planning postpartum glucose testing.

Supported By: International Diabetes Federation

1368-P

To What Extent May We Trust Patient-Generated Blood Glucose Diary Records in Gestational Diabetes Mellitus?

EMMANUEL COSSON, BAZ BAZ, FRANÇOISE GARY, MIHAELA DOCAN, DORIAN SANDRE-BANON, CAMILLE CUSSAC-PILLEGAND, ISABELA BANU, SABRINA CHIHEB, YAHYA JABER, PAUL VALENSI, *Bondy, France, Paris, France*

Self-monitored blood glucose (SMBG) is crucial during gestational diabetes mellitus (GDM) to make clinical decisions, like initiating antidiabetic drug in addition to diet. We aimed to evaluate the reliability of patient-generated blood glucose diary records in women with GDM. We prospectively selected women with newly-diagnosed GDM who were referred to a diabetes management program, spoke national language and had understood glycaemic goals before (≤95 mg/dL) or 120 minutes after meal (≤ 120 mg/dL); and how (with the same device including a post-prandial alarm), when (6 times a day) and why to perform SMBG measurements. During the first follow-up visit, we collected SMBG results from glucometers and diary records. The women were not aware of the objectives of the study. Data were analyzed over 12.7±2.9 days in 97 women. A total of 68, 54 and 50% of subjects had actually performed at least 90% of required measurements at fasting, after meals and both, respectively. Delay between measurements before and after meal was 148±29 minutes on average (minimum 59; maximum 238); with only 21.4% of the women performing 90% of post prandial measurements 100 to 140 minutes after meals. Overall concordance between values reported in the diary records and meter memory values was 95.0±9.2%; 27% of the women had written at least one unmeasured glucose value on their diary records (minimum 1; maximum 27). The proportion of women who, more than three times a week, underestimated above goal their glucose values or did not report a high glucose value was 10.2%. To conclude, between instauration of SMBG and first visit, only half of the women with GDM, although selected in this study, performed 90% of expected measurements, with almost 80% of post-prandial measurements delayed more than 20 minutes. In around 10% of patients, generated SMBG diary records were not reliable to change/adapt treatment. Exploring glucometer memory during visit or using automatic diary records may improve GDM care management.

Supported By: Roche Diagnostics

1369-P

Effects of Insulin Therapy on Pregnancy Outcomes in Women with Gestational Diabetes Mellitus Diagnosed Using IADPSG Criteria

DELIA BOGDANET, AOIFE M. EGAN, ORATILE KGOSIDIALWA, BRIDA KIRWAN, LOUISE CARMODY, FIDELMA DUNNE, *Galway, Ireland*

In Ireland the prevalence GDM using the IDPSG criteria is 12.4%. 40% of these women require insulin to achieve target glucose levels in the Irish setting. The aim of this study was to assess the effect of insulin on preg-

For author disclosure information, see page A696.

nancy outcomes in women with GDM and determine if the outcomes are comparable to women with normal glucose tolerance (NGT). This retrospective cohort study included 752 women with insulin treated GDM and 2496 women with NGT during pregnancy. All women were from the ATLANTIC DIP network database. Maternal outcomes examined were preeclampsia, antepartum (APH) and postpartum hemorrhage (PPH), pregnancy-induced hypertension (PIH), polyhydramnios. Fetal outcomes examined were neonatal hypoglycemia, neonatal mortality, admission to neonatal intensive care unit (NICU), macrosomia, large for gestational age (LGA) and small for gestational age (SGA). Infants of women with insulin treated GDM were more likely to be hypoglycemic at birth (aOR 7.27, 95% CI 2.49- 21.22) and more likely to require admission to NICU (aOR 13.90 95% CI 10.23- 8.87). Neonatal mortality, rates of macrosomia, LGA and SGA infants (median birth weight+/-sd 3.58+/-0.6 GDM, 3.57+/-0.5 NGT, p=0.81) were similar to women with NGT. Women with GDM had a higher BMI (BMI >30 64.19% GDM; 20.41% NGT, p<0.01), a higher rate of family history of DM (68.05% GDM; 31.91% NGT, p<0.01) and a greater history of smoking (11.79% GDM; 6.89% NGT, P<0.01). Rates of preeclampsia, PIH, APH and PPH were similar between women with insulin treated GDM and NGT. Women with GDM had a higher risk of polyhydramnios (aOR 8.52 95% CI 4.40-16.47). Insulin treatment for women with GDM is successful in normalizing rates of macrosomia, LGA and SGA and maternal hypertensive disorders. Neonatal hypoglycaemia and polyhydramnios are excessive but this may reflect ascertainment bias. Despite these positive outcomes admission to NICU remains excessive and this warrant's further investigation.

1370-P

Gestational Diabetes Mellitus, Screening Practices, and Association with Social Deprivation: Data from the 788,494 Women Who Delivered in France in 2013

NOLWENN REGNAULT, ELODIE MOUTENGOU, SANDRINE FOSSE-EDORH, YAYA BARRY, CÉCILE BILLIONNET, ALAIN WEILL, JEAN-JACQUES ALTMAN, ANNE VAMBERGUE, EMMANUEL COSSON, *Saint Maurice, France, Paris, France, Lille, France, Bondy, France*

In 2010, French guidelines endorsed the IADPSG criteria and risk-factor based screening for gestational diabetes mellitus (GDM). In 2011, GDM prevalence was 6.4%. Our objectives were 1. to describe, in France in 2013, GDM prevalence and evolution, screening rates for GDM, and for type 2 diabetes (T2D) after pregnancy among women with GDM, 2. to investigate potential socioeconomic disparities. Using the national health insurance information system, we included all deliveries and pregnancy termination after 22 gestation weeks (GW) in France in 2013. The database includes all reimbursed drugs, biological tests, hospitalizations and a deprivation index of the town of residence. We sequentially identified preexisting diabetes and GDM based on reimbursements (insulin, oral antidiabetics, HbA1c, test strips) before, during and after pregnancy and hospital diagnosis codes. Among women without preexisting diabetes, 62.6% underwent GDM screening before 24 GW, and 37.0% an OGTT between 24 and 28 GW. GDM prevalence was 8.6%. After pregnancy, 20.1% were tested for T2D within 3 months and 52.4% within 1 year. GDM prevalence and screening increase with deprivation while T2D screening decreases. To conclude, GDM is increasing in France and, in 2013, screening rates were rather high during pregnancy, but not so after, with gradients according to social deprivation.

Table. GDM Screening, Prevalence and Postpartum Screening for T2D According to the Fdep Deprivation Index.

Quintiles of social deprivation	GDM screening (1st and/or 2nd trimester) in women without preexisting diabetes (%) (N= 785,596)	GDM prevalence in women who delivered after 22 GW (%) (N= 788,494)	Screening for T2D within 3 months after delivery among women diagnosed with GDM (%) (N=65,560)
All	62.6	8.6	20.1
1st quintile (least deprived)	59.7	8.0	23.5
2nd quintile	61.9	8.3	23.3
3rd quintile	64.4	8.3	19.8
4th quintile	64.8	8.8	18.6
5th quintile (most deprived)	64.6	9.7	18.1
P for trend	<0.0001	<0.0001	<0.0001

1371-P

Outcomes of Twin Pregnancies Complicated by Gestational Diabetes: A Meta-analysis of Observational Studies

RACHEL T. MCGRATH, SAMANTHA L. HOCKING, EMMA S. SCOTT, GREG R. FULCHER, SARAH J. GLASTRAS, *Sydney, Australia*

Gestational diabetes mellitus (GDM) in singleton pregnancy is associated with large for gestational age (LGA) babies and adverse neonatal outcomes, which can be reduced by identification and subsequent treatment of GDM. However, the impact of GDM in twin pregnancy is unclear. Importantly, the treatment of GDM in twin pregnancy may lead to an increased risk of small for gestational age (SGA), which is a common complication of twin pregnancy, alongside prematurity. In order to explore the impact of GDM in twin pregnancy on neonatal outcomes, we carried out a meta-analysis of observational studies. Studies investigating the impact of GDM in twin pregnancy on birth weight and/or neonatal outcomes were identified through an online search of 3 databases. Random-effects models with inverse variance weighting were used to calculate unadjusted odds ratios (OR). Eleven studies (comprising 12,777 women) were included in the analyses. There was no difference in birth weight or gestational age at delivery for twins born to women with and without GDM. A trend towards an increased risk of LGA was found for twins of mothers with GDM (OR 1.31; p = 0.06). Conversely, GDM in twin pregnancy was significantly associated with a lower risk of SGA (OR 0.80; p = 0.002). There was no correlation between GDM in twin pregnancy and respiratory distress or neonatal intensive care unit (NICU) admission, however a reduced risk of low APGAR score was observed in GDM twin pregnancy (OR 0.69; p = 0.02). Unlike in singleton pregnancy, GDM in twin pregnancy does not significantly increase the incidence of LGA and protects against SGA. This data suggests that the adverse neonatal outcomes associated with GDM in singleton pregnancy are not observed in twin pregnancy. Therefore, the impact of identifying and treating GDM in twin pregnancy warrants further investigation.

1372-P

A Longitudinal Study of Antenatal and Postpartum Depression and Gestational Diabetes (GDM) Risk: Untangling the Bidirectional Relation in a Multiracial Cohort

STEFANIE N. HINKLE, GERMAINE BUCK LOUIS, PAUL ALBERT, SHRISTI RAWAL, YEYI ZHU, CUILIN ZHANG, *Rockville, MD*

Depression has been linked to diabetes among non-pregnant individuals; however, which comes first and whether this applies to GDM is less understood. In the NICHD Fetal Growth Study (n=2466), a prospective cohort of women without psychiatric disorders or diabetes before pregnancy, we examined the relations of antenatal and postpartum depression (PPD) with GDM risk. GDM was diagnosed by medical record review. Depression was assessed in the 1st [8-13 gestational weeks] and 2nd (16-22 weeks) trimesters and 6 weeks postpartum using a validated scale. In a subset of the cohort, PPD was defined as a score ≥10 or anti-depression medicine use after delivery among GDM cases (n=102) and controls (n=101). Logistic regression was used to estimate adjusted odds ratios (aOR) (95% confidence intervals (CI)) for the association of antenatal depression (in quartiles) with GDM, and GDM with PPD adjusting for sociodemographic, prepregnancy BMI and other risk factors. Greater antenatal depression was related to an increased GDM risk, although the association became statistically insignificant after adjusting for other risk factors; the aOR comparing the highest vs. lowest quartile was 1.68 (95% CI 0.81-3.45) in the 1st and 1.63 (95% CI 0.80-3.31) in the 2nd trimester. Furthermore, women with high depression scores (the highest quartile) in both the 1st and 2nd trimesters had more than 4-fold (95% CI 1.24-14.40) elevated GDM risk than those in the lowest quartile in both periods, but this was attenuated slightly to 3.71 (95% CI 0.95-14.74) and became marginally significant after the adjustment of other risk factors. GDM was related to an adjusted 5-fold (95% CI 1.09-22.82) elevated PPD risk. In this healthy pregnant cohort, there was suggestive evidence that greater depression in early pregnancy, in particular depression persisting into the 2nd trimester was related to an elevated GDM risk. GDM was related to a greater risk of postpartum depression.

1373-P

ATLANTIC DIP: An Evaluation of Women with Type 1 and Type 2 Diabetes at 12 Months Postpartum

AOIFE M. EGAN, LOUISE CARMODY, BREDA KIRWAN, FIDELMA P. DUNNE, *Galway, Ireland*

During pregnancy women with diabetes are highly motivated and typically receive intensive specialist care. Those who attend prepregnancy care benefit from additional input. This study sought to assess the impact of pregnancy on diabetes treatment goals. We hypothesised that intensive management during pregnancy would result in a sustained improvement postpartum. We included women with type 1/2 diabetes who attended 3 centres along the Irish Atlantic Seaboard for antenatal care from 2006-2014. Women were evaluated at 6 months prepregnancy (or at first prepregnancy care visit), and 12 months postpartum. In total 269 were included, 177 (66%) with type 1 and 92 (34%) with type 2 diabetes. 117 (44%) attended prepregnancy care. At 12 months postpartum, 70 (26%) were attending prepregnancy care, 26 (9.7%) were pregnant, 40 (14.9%) were lost to follow up and 133 (49.5%) were attending general diabetes clinics. Despite achieving tight glycaemic control in the first trimester of pregnancy (HbA1c 7.2±1.6%), there was no difference in HbA1c before and 12 months after pregnancy (before:7.8±1.9%, after:7.6±1.7%, p=0.26). Furthermore, there was no difference in mean systolic/diastolic blood pressure (SBP/DBP), lipid profile, albumin-creatinine ratio or weight in women before and after pregnancy. At 12 months postpartum, those who attended prepregnancy care had a lower SBP (119.8±17.0 mmHg vs. 126.3±14.6 mmHg, p=0.001), DBP (74.8±8.0 mmHg vs. 77.6±9.9 mmHg, p=0.04) and weight (75.0±14.4 kg vs. 81.0±20 kg, p=0.04). Finally, women who achieved a first trimester HbA1c of <7.0% continued to demonstrate superior glycaemic control postpartum (6.8±1.3% vs. 8.4±1.8%, p<0.001). Despite intensive education and personal motivation during pregnancy, women with diabetes do not have a sustained improvement in diabetes control at 12 months postpartum. While the subset who attended prepregnancy care had better metabolic parameters postpartum, there exists a challenge to motivate all women in the postpartum period.

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1374-P

Breastfeeding Duration and Postpartum Weight Retention after GDM Pregnancy

REENA OZA-FRANK, RASHMI KACHORIA, *Columbus, OH*

Many studies indicate that extended breastfeeding duration may decrease maternal weight retention in the first year postpartum. However, none have examined the association between breastfeeding duration and exclusivity and weight retention at 1 year postpartum after gestational diabetes mellitus (GDM) pregnancy. We used data from the 2005-2007 Infant Feeding Practices Study II (n=115). Women completed monthly questionnaires on infant feeding through 1 year. The main outcome variable was calculated as the difference between mother's self-reported prepregnancy weight collected in the last trimester of pregnancy and her self-reported weight collected at 1 year postpartum. Breastfeeding duration was defined as the age of the infant in weeks when the mother completely stopped breastfeeding or pumping milk, to estimate the length of time the mother was lactating and therefore expending calories producing milk. Exclusive breastfeeding was defined as breast milk consumption only. To examine the association between breastfeeding duration and exclusivity and weight retention, we used multivariable linear regression. Women retained 0.39 pounds (Standard Deviation=16.3) between prepregnancy and 1 year postpartum. Almost half of women lost weight (mean 13.8 pounds (10.4)), and breastfed for 29.5 weeks (23.3) and exclusively for 5.6 (9.0); 43.5% of women gained weight (12.9 (10.3)), and breastfed for 18.9 weeks (20.1) and exclusively for 2.4 (6.0); 7% reported no change in weight, and breastfed for 18.9 weeks (22.9) and exclusively for 0.4 weeks (1.2). In adjusted analyses, any (β=-.14, p=.047) and exclusive breastfeeding (β=-.53, p=.01) were inversely associated with postpartum weight retention. Women with GDM history are 7 times more likely to develop type 2 diabetes over their lifetime compared to women without the same history. Even modest weight loss is effective for type 2 diabetes prevention, supporting the need to focus on increasing lactation duration as an early intervention.

EPIDEMIOLOGY—AGING

Moderated Poster Discussion: Epidemiology of Aging *(Posters: 1375-P to 1382-P), see page 17.*

1375-P

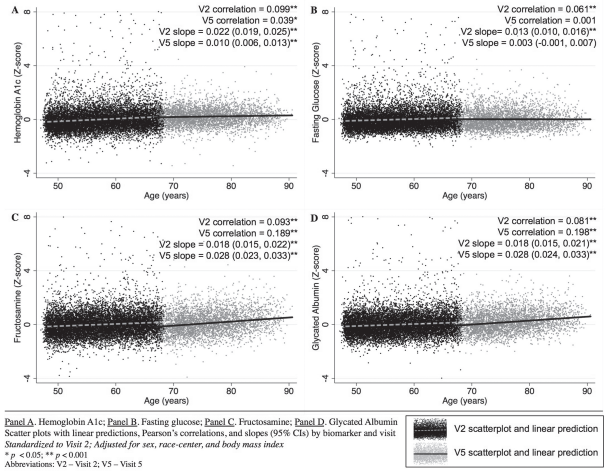
Age-related Changes in Hyperglycemia: A Comparison of Biomarkers of Hyperglycemia

BETHANY WARREN, ANDREEA RAWLINGS, ALEXANDRA K. LEE, CHRISTINA PARRINELLO, JOSEF CORESH, ELIZABETH SELVIN, *Baltimore, MD, Bronx, NY*

The American Diabetes Association's 2016 Standards of Medical Care in Diabetes state that age should be taken "into consideration" when diagnosing diabetes. It is as of yet unclear how this recommendation might be actualized. Observed age-related elevations in A1c are a source of controversy, with some experts arguing that increases may be a result of non-glycemic factors. To inform this issue, we examined the relationship of age with four biomarkers of hyperglycemia: A1c, fasting glucose (FG), fructosamine, and glycated albumin (GA). In this serial cross-sectional study, we included ARIC study participants without diagnosed diabetes at visit 2 in 1990-92 (n=11,668; age range: 47 to 70 years) and visit 5 in 2011-13 (n=3,884; age range: 67 to 91 years). To understand differences by age, for each biomarker we generated scatterplots, calculated Pearson's correlations, and performed linear regression with z-scores to allow for comparison.

Values of A1c, fructosamine, and GA were higher at older ages, with increases in a monotonic fashion, while FG values were more variable and increased during middle age (visit 2), but not older ages (visit 5; Figure). Consistent with other studies, we observed age-related increases in A1c but also saw comparable increases in other biomarkers of hyperglycemia, suggesting that age-related changes in A1c may primarily reflect true increases in the prevalence of hyperglycemia in aging.

Figure. Glycemic Markers and Age (Visit 2: 1990-92 and Visit 5: 2011-13).



Panel A. Hemoglobin A1c; Panel B. Fasting glucose; Panel C. Fructosamine; Panel D. Glycated Albumin
Scatter plots with linear predictions, Pearson's correlations, and slopes (95% CIs) by biomarker and visit
Standardized to Visit 2; Adjusted for sex, race-center, and body mass index
* $p < 0.05$; ** $p < 0.001$
Abbreviations: V2 – Visit 2; V5 – Visit 5

1376-P

Racial Differences in Potential Overuse of Glucose-Lowering Medication among Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

ALEXANDRA K. LEE, A. RICHEY SHARRETT, B. GWEN WINDHAM, ELBERT S. HUANG, ELIZABETH SELVIN, *Baltimore, MD, Jackson, MS, Chicago, IL*

Rates of hypoglycemia are significantly higher for blacks than whites but the reasons for this disparity are unknown. One potential explanation is overtreatment among blacks, defined as ongoing use of medications known to increase risk of hypoglycemia despite achievement of low A1c and presence of hypoglycemia risk factors. We conducted a cross-sectional analysis of 1,837 older black and white persons with diagnosed diabetes in the ARIC study in 2011-2013 (age range: 67-89, 32% black). In those with A1c <7%, we examined the prevalence of established risk factors for hypoglycemia and estimated the age- and sex-adjusted odds of taking high-risk medications (insulins, sulfonylureas, and/or meglitinides) in blacks vs. whites using logistic regression. Of 1311 persons with A1c <7%, mean age was 76 years, 29% were black, and median duration of diabetes was 7.9 years (25th and 75th quartiles: 4.4 - 12.3). The use of high-risk medications was common among and similar between blacks and whites with risk factors for hypoglycemia (Table). Blacks with one or no risk factors were more likely to use high-risk

For author disclosure information, see page A696.