CLINICAL THERAPEUTICS/NEW TECHNOLOGY—GLUCOSE MONITORING AND SENSING

2185-PO

WITHDRAWN

2186-PO

Average Daily Risk Range in Young Children with Type 1 Diabetes: Comparing Risk Scores Generated from Continuous Glucose Sensing Versus Self-Monitoring Data

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Young children with type 1 diabetes (T1DM) are susceptible to more extreme glucose variability than older patients because of their high sensitivity to insulin and variable routine (e.g., impacting activity levels and carbohydrate intake). The average daily risk range (ADRR) is a glucose variability measure developed using self-monitoring blood glucose data (SMBG) in adults with T1DM. ADRR identifies risk for glucose excursion using the following scale: <20 low risk, 20-40 moderate risk, >40 high risk. In this study, we examined ADRR values for young children with T1DM using both continuous glucose monitoring (CGM) and SMBG data. We hypothesized that in young children 1- the ADRR levels calculated from CGM (ADRRc) would reflect greater variability than the ADRR levels calculated from SMBG (ADRRs); 2- because ADRRc levels would reflect greater variability, ADRRc would show better concurrent validity with children's mean amplitude of glucose excursion scores (MAGE) than ADRRs levels. Forty-eight young children (5.1±1.2 years) participated. SMBG data were collected for 14 days including the period of CGM (92±37 SMBG readings). Mean duration of CGM trace was 65±19 hours (782±228 CGM readings). Children had a mean ADRRc of 55±12 and a mean ADRRs of 46±11, suggesting they are at high risk for excursion. Comparing ADRRc and ADRRs, approximately 40% of young children had a mismatch in their ADRR category and 74% of the time the ADRRc reflected higher risk than the ADRRs. Specifically, 83% of young children had an ADRRc >40, compared to 69% using their ADRRs. We found a significant correlation between young children's ADRRc levels and MAGE scores (r= 0.71, p=0.01), but not between their ADRRs and MAGE scores (r=0.17, p= 0.24). In young children with T1DM, ADRR scores calculated using CGM data appear to identify greater risk for glucose excursion and to have better concurrent validity with children's MAGE scores than ADRR scores calculated using SMBG. Thus, to study glucose variability in young children with T1DM, CGM data may provide a better assessment of risk for glycemic excursion than SMBG data.

2187-PO

Breath/Plasma Gas Concentration Ratio as a Possible Key Determinant of Breath-Based Glucose Measurement

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Alternative, non-invasive testing methods for plasma glucose, insulin, and lipids could greatly enhance diabetes/obesity management. The feasibility of reasonably accurate, non-invasive breath testing for plasma glucose and related variables was previously shown by our group. Current use of the technique, however, hinges on the concept that exhaled breath reflects peripheral metabolism through a constant, unchanging ratio of gas concentrations between plasma and breath. This ratio, for gases implicated in carbohydrate metabolism, has never been systematically studied, and may differ across gases and, in the same gas, across metabolic conditions. Fully clarifying these concepts is likely to considerably enhance the accuracy of our current breath-based predictive models for plasma glucose. Therefore, we developed a novel apparatus to completely degas plasma via a constant flow of helium micro-bubbles; extracted gases were quantified with gas chromatography/mass spectrometry. We used the device to analyze 14 matched breath and plasma samples (from 7 healthy males, 23.7±1.1yrs, sampled twice one week apart), and determined the breath/plasma ratio of 75 compounds. Among these, representative ketones and hydrocarbons potentially involved in carbohydrate metabolism are shown in figure. Our data suggest a complex interaction between peripheral tissue gas production and exhaled breath concentrations, with different gases displaying greater concentrations in breath (methanol, acetone) or plasma (butanone, *n*-nonane, and *n*-decane). The complete understanding of the relationship between gas concentrations in plasma and breath will further advance the potential for a non-invasive, portable breath device to facilitate the diagnosis, management, and prevention of cardiovascular complications.

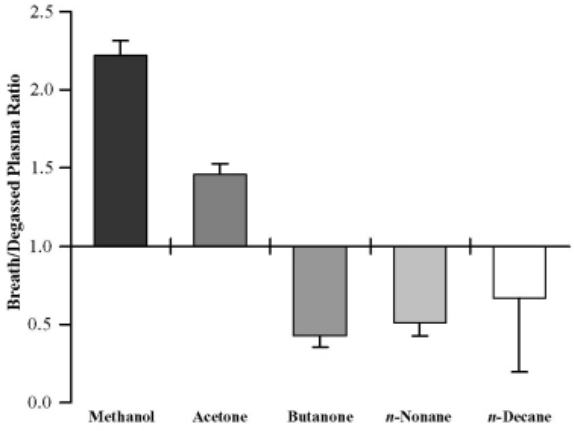

Figure. Breath/Degassed Plasma Ratio: methanol, acetone (greater in breath than plasma); butanone, *n*-nonane, and *n*-decane (greater in plasma than breath). Data are mean±SEM from 7 healthy males.

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2188-PO

Burden of Sliding Scale Insulin Use in Elderly Long-Term Care Residents with Type 2 Diabetes

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Sliding scale insulin (SSI) therapy provides a suboptimal approach to glycemic control. Despite its limitations, SSI is commonly used for patients with type 2 diabetes mellitus (T2DM) in the long-term care (LTC) setting. This retrospective study assessed the burden associated with SSI use in elderly patients with T2DM in selected LTC facilities in the United States using medical chart data merged with the Minimum Data Set (MDS) assessment.

Patients were included if they were admitted to a LTC facility, stayed for ≥3 months, had ≥1 full MDS assessment, had insulin dispensed on ≥2 occasions with no insulin pump use, and were not comatose or in hospice care during their LTC stay. Data were descriptively analyzed to provide a summary of preliminary findings from an initial sample of patients meeting the study inclusion criteria.

In the first wave of the study, 29 patients from 3 facilities were identified. Patients had an average of 3-months follow-up (62% female, 59% white, mean [±SD] age of 77 ± 11.5 years, 83% having ≥1 HbA1c value recorded, mean [±SD] HbA1c 6.6 ± 1.0%, 67% with HbA1c ≤7%, and mean [±SD] fasting blood glucose 137 ± 39 mg/dL). Almost all patients (n=28) were on a SSI regimen for the entire duration of follow-up, and 35% (n=10) were on a SSI regimen exclusively. On average, patients received 22 ± 6.9 SSI-related finger sticks per week, and of these an average of 16 ± 7.4 finger sticks (73% of all finger sticks administered) did not result in insulin administration because the blood glucose was below sliding scale threshold levels.

Despite patients in this study maintaining good glycemic control, SSI use was widespread in the LTC facilities examined and was associated with an unnecessarily high finger stick burden among elderly T2DM patients. These preliminary findings question the necessity of prolonged SSI therapy among LTC elderly patients with T2DM.

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2189-PO

Clinical Accuracy of Time-Delayed Laboratory Glucose Measurements

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Infusion of rapid-acting insulin requires accurate glucose measurements in order to target euglycemia while minimizing the risk of hypoglycemia. Lab measurements based on venous blood draws are the most common method for glucose measurement. However, lab measurements are not typically available in real time. In practice, processing times associated with lab measurements can be 15 minutes or longer, whereas strip-based glucose meters and continuous glucose sensors provide glucose readings

For author disclosure information, see page 785.

within seconds. This study assesses the impact of processing delays on the effective clinical accuracy of lab measurements.

Lab measurements using a YSI glucose analyzer were obtained from venous blood every 15 minutes for 36 hours from each of 58 T1 subjects. During 15% of each 36 hours, insulin and glucose challenges (median absolute rate of change = 2 mg/dL/min) were performed. To simulate delayed lab results, each YSI value from each subject was paired with those from earlier time intervals (15, 30, 45, or 60 minutes prior). To assess the clinical accuracy of a delayed YSI result relative to a real-time result, the percentage of YSI pairs that meet the ISO 15197:2003(E) standard for glucose measurement accuracy (+/- 15 mg/dL for BG <= 75 mg/dL, +/- 20% for BG > 75 mg/dL) was calculated for each delay interval.

Processing delays in lab measurements were shown to degrade effective clinical accuracy as time delay increased. Lab results delayed by 15 minutes do not meet the ISO 15197 accuracy standard of 95%.

This analysis suggests that processing delays as short as 15 minutes can impact the clinical relevance of results, due to glucose fluctuations. Real-time meters and sensors may be more appropriate for acute treatments to control glucose. Since this retrospective analysis was performed on a study with ambulatory T1 adults subjected to insulin and glucose challenges, the findings may not be directly applicable to other populations. Delayed laboratory glucose measurements should be used with caution when used to make acute diabetes treatment decisions.

Delay (minutes)	# Pairs	ISO15197
15	20188	91.3%
30	19828	77.6.%
45	19461	66.0%
60	19188	57.5%

2190-PO

Determinants of the Accuracy of Continuous Glucose Monitoring in Non-Critically Ill Patients with or without Heart Failure Receiving an Insulin Infusion

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Continuous glucose monitoring (CGM) may be useful in hospitalized patients outside of the ICU, where less intensive nursing resources available and fewer variables affecting accuracy may be present. The objective of this study was to examine the accuracy and utility of CGM in non-critically ill hospitalized patients with or without heart failure (HF) who were receiving an insulin infusion.

Subjects in 2 groups wore an I-Pro CGM for at least 24 hours. Group 1: patients with HF exacerbation receiving an insulin infusion as part of a randomized study. Group 2: non-ICU patients without HF receiving an insulin infusion for uncontrolled hyperglycemia. Capillary glucose was measured using the Accu-check Inform glucometer.

Eleven patients in Group 1 and 16 patients in Group 2 were included. The admission glucose for the two groups differed as expected (202 vs. 509 mg/dl, p<0.001) but the first sensor glucose (146 vs. 178 mg/dl, p=0.2) and time to initiation of the sensor did not differ. Continuous glucose error grid analysis showed that 99% of paired readings between 70 and 180 mg/dl were in zone A (clinically accurate), but there were significantly fewer accurate readings in the hyperglycemic and hypoglycemic range. There was no difference by CHF status. The correlation coefficient for group 1 was 0.91 and for group 2 was 0.85 with a mean absolute meter-sensor (M-S) difference (MAD) of 13.5 and 27.3, respectively. Analyzing MAD by glucose category (<100, 100-150, 151-200,>200 mg/dl) in all M-S pairs showed a significant increase in MAD with increasing glucose. However, MAD was higher in group 2 compared to group 1, even after accounting for glucose category. In univariable analysis, lack of HF, greater age, admission glucose, HbA1c and creatinine were significantly associated with MAD. Linear regression models showed that only admission glucose was a significant predictor of MAD.

The results demonstrate that baseline glucose, but not HF, has a prolonged effect on CGM reliability and should be taken into count in the future application of 'real-time" CGM in the hospital.

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2191-PO

WITHDRAWN

2192-PO

GlyCEDIA Study—Glycemic Control Evaluation Study in Hemo-Dialysed Patients Receiving Insulin Analogues

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Introduction: Appropriate management of glycemic control in a group of hemodialysed patients with type 2 diabetes (T2D) is crucial to reduce cardiovascular mortality and morbidity, but remains difficult to achieve in such patients submitted to dialysis sessions three times a week. Continuous glucose monitoring (CGM) is a useful clinical tool to optimize glucose level control.

Objective: To evaluate the glycemic control in hemodialysed patients with type 2 diabetes under optimized insulin therapy, by means of CGM.

Subjects and methods: A prospective multicenter 3 months study in hemodialysed patients with T2D under optimized insulin treatment (prandial plus basal insulin: aspart-detemir Novo-Nordisk). Evaluation parameters: mean predialysis venous blood glucose, A_1c hemoglobin, 48 hours CGM (Navigator®, Abbott) including two consecutive dialysis sessions realized at 0, 1 et 3 months, mean interstitial glucose concentration, mean amplitude of glycemic excursions (MAGE) and coefficient of glycemic variation (CV). Insulin treatment was adjusted three times according to CGM values.

Results: From January 2010, 13 patients were included. The analysis concerns the first 6 patients (2 women and 4 men, age = 65,5±9,5 years, BMI = 31±6 kg/m^2, duration of T2D = 16,5±7 years), dialyzed for 3,1±1,8 years. After 3 months observation: A1c hemoglobin decreased from 7,7±1,0% to 7,3±0,9% without nocturne hypoglycemic events. Predialysis venous blood glucose decreased from 9,1±4,28 mmol/l to 7,1±2,7 mmol/l, mean interstitial glucose of the CGM decreased significantly from 9,9±3,0 to 8,6±2,83 mmol/l (p=0,09). MAGE decreased from 5,94 to 5,5 mmol/l. The data from 18 CGM show that the MAGE, but not CV, was significantly correlated with the mean glucose level (p<0,001).

Conclusion: In hemodialysed patients with T2D under optimized insulin treatment, CGM analysis showed an improvement in glucose control without increase in nocturne hypoglycemia after 3 months. MAGE and CV gave different informations confirming the interest of CGM in this population of T2D patients.

2193-PO

Glycemic Variability and Metabolic Control in Patients with Diabetes Mellitus: Significance of Indicators Obtained with Continuous Glucose Monitoring (CGM)

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Little evidence is available on the relationship between HbA1c and indicators of glycemic variability. The aim of this study was to investigate the correlation between HbA1c and several parameters of glycemic control, hyperglycemia, and glycemic variability in Type 1 and Type 2 diabetic patients.

We studied 68 subjects divided into 3 groups: 35 had type 1 diabetes (group 1); 17 had type 2 diabetes on multiple daily insulin injections (MDI) (group 2); and 16 had type 2 diabetes treated with oral hypoglycemic drugs and/or basal insulin (group 3). Data were obtained with the MiniMed Continuous Glucose Monitoring System (CGMS) used consecutively for at least 48 hours. HbA1c was measured at the baseline and after monitoring. Glycemic control was assessed from the average glucose (AG) and the total area under the curve (AUC tot); hyperglycemia, measuring the postprandial AUC and the AUC over 140; glycemic variability indicators were the standard deviation (SD), the mean amplitude of glycemic excursion (MAGE), the low blood glycemic index (LBGI), the high blood glycemic index (HBGI), and the blood glucose rate of change (BG ROC).

The results showed a close correlation between HbA1c and the hyperglycemia parameters (AG and AUC tot). Among the indicators of glycemic variability, only HBGI and SD correlated closely with HbA1c, whereas BG ROC and LBGI values predictive of a high variability and high hypoglycemic risk were not found to affect HbA1c levels. For the same of HbA1c levels, glycemic variability was greater in patients with longstanding disease. Among the parameters considered, the MDI regimen appeared to correlate best with the glycemic profile and was associated with a greater glycemic variability in both types of diabetes.

HbA1c levels seem to be affected by sustained hyperglycemia and not by hypoglycemia or marked glycemic variability, which limits their value as a "gold standard" indicator of glycemic control. The glycemic variability indicators considered were more accurate than HbA1c in showing the worsening of glycemic control, typical of longstanding diabetes and associated with the MDI regimen.

2194-PO

Haematocrit Performance of the OneTouch® Verio™ Pro Blood Glucose Monitoring System

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A study was performed to determine the haematocrit (hct) performance of the OneTouch® Verio™ Pro Blood Glucose Monitoring System (BGMS). Hct is a common interferent of self-monitoring blood glucose (SMBG) systems, which measure glucose in whole blood and provide plasma equivalent results. Hct introduces a systematic bias dependent upon the erythrocyte content of the sample.

The system includes an electrochemical test strip design featuring co-facially arranged thin-film gold and palladium electrodes, coupled to a complex waveform with three distinct phases in which sequential positive and negative potentials are applied. The resultant current response profiles are algorithmically interrogated to provide high accuracy blood plasma glucose values with minimum sensitivity to hct.

Performance was assessed on venous blood samples from 3 donors. Each sample was adjusted to yield 5 target hct levels (19-61%) and 5 target glucose levels (30-560 mg/dL). Tests were performed on 12 meter devices with 3 test strip lots and results compared against a laboratory reference method (YSI 2300).

For all test combinations (donor, hct, glucose and test strip lot), 100% (2700/2700) of results were within the ISO 15197 error tolerance (±20% of reference result at glucose ≥ 75 mg/dL; ±15 mg/dL at glucose < 75 mg/dL), whilst 99.8% (2698/2700) of results were within ±15% of reference result (glucose ≥ 80 mg/dL) or ±12 mg/dL (glucose < 80 mg/dL). Mean bias values were <5% or <5 mg/dL for all hct/glucose combinations, with a trend from positive to negative bias with increasing glucose concentration (Table). The most extreme bias, -17.7%, was observed at 61% hct and 560 mg/dL glucose.

Table: System haematocrit performance: Mean bias breakdown by hct level and glucose (n=108 per each glucose/hct combination). Bias expressed as mg/dL for two lowest glucose levels and percentage for higher levels.

Hct (%)	Glucose level (mg/dL)				
	30	65	240	450	560
19	1.32	-0.90	0.87	-2.41	-4.16
30	1.22	-1.50	-1.77	-3.48	-4.67
40	1.06	1.16	-2.21	-2.30	-3.55
50	2.66	2.60	1.03	-3.47	-2.60
61	3.64	3.04	-3.37	-4.26	-4.15

2195-PO

How Is Fructosamine Affected by Urinary Albumin Excretion?

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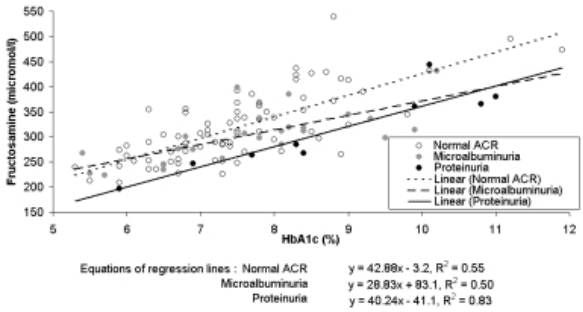
Fructosamine derived from glycated albumin can be used to monitor glycaemia when HbA_{1c} is inappropriate. A low fructosamine relative to blood glucose, was observed in a patient with proteinuria. We investigated the effect of albuminuria (albumin/creatinine ratio, ACR) on relationships between fructosamine, HbA_{1c} and random plasma glucose (RPG).

HbA_{1c} was measured by IE HPLC and an IFCC secondary reference method in patients attending a university hospital diabetes clinic, n=134, aged 60(50 to 71)years, median(IQ range), 25% had Type 1 diabetes, 68% male, 76% white Caucasian, 13% South Asian, 8% Afro-Caribbean and 3% other ethnicities.

Fructosamine was 304(269 to 353)μmol/l, n=131, HbA_{1c} 7.5(6.8 to 8.4)%, n=134, and RPG 8.8(6.7 to 12.4)mmol/l, n=108 with 24% (28/115) having microalbuminuria, ACR men >2.5, women >3.5g/mol, and 8% (9/115) proteinuria, ACR >30g/mol. Treatment was unchanged over the previous 3 months in 92% with 43% on insulin, 23% oral agents and 33% on both. Nephropathy was recorded in 11% (14/131).

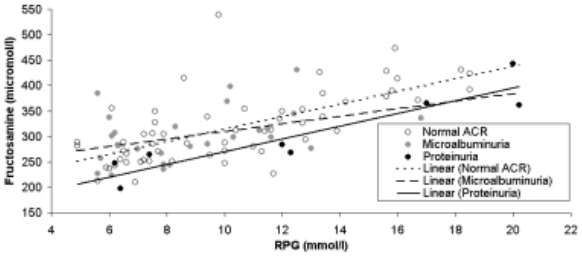
There were no significant differences between the slopes of linear regression lines but for fructosamine vs HbA_{1c} (Fig 1), the normal ACR line was higher than both the microalbuminuria, p=0.045, and proteinuria lines, p<0.001, and vs RPG (Fig 2) significantly higher than proteinuria, p=0.024.

Figure 1 : Fructosamine versus HbA1c



Equations of regression lines : Normal ACR $y = 42.88x - 3.2$, $R^2 = 0.55$
Microalbuminuria $y = 26.83x + 83.1$, $R^2 = 0.50$
Proteinuria $y = 40.24x - 41.1$, $R^2 = 0.83$

Figure 2 : Fructosamine versus RPG



Equations of regression lines : Normal ACR $y = 12.38x + 190.6$, $R^2 = 0.45$
Microalbuminuria $y = 7.45x + 235.2$, $R^2 = 0.16$
Proteinuria $y = 12.52x + 144.7$, $R^2 = 0.85$

In patients with proteinuria, fructosamine maybe an unreliable measure of glycaemia. Microalbuminuria may also depress fructosamine relative to glucose. The effect of urinary albumin excretion on this surrogate marker deserves further investigation.

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2196-PO

Impact of OneTouch Diabetes Management Software (OTDMS) on Physician-Patient Discussions

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An observational, pilot study was performed to evaluate if use of OTDMS impacts physician-patient interaction and decision-making. Cameras were placed in exam rooms and interactions were recorded between 6 community-based endocrinologists and 24 patients during follow-up visits. 12 patients brought OneTouch blood glucose (BG) meters and had these downloaded into OTDMS; 12 brought written BG records.

Patient Demographic Information	OTDMS Visits (n=12)	Paper Log Visits (n=12)
Mean age (range)	52 (30-72)	65 (43-73)
Gender (male)	4 (33%)	6 (50%)
Rate diabetes as "well controlled"	5 (42%)	2 (17%)
Type 2 diabetes	11 (92%)	12 (100%)
Use Insulin	8 (67%)	9 (75%)
Employed full-time	7 (58%)	1 (8%)

Post-visit, written surveys were completed by patients and physicians. Recordings were transcribed and analyzed using sociolinguistic techniques, and interactions were compared between the 2 groups.

Total discussion times were similar, whether data was reviewed from OTDMS or logbooks (average 14.60 vs 14.07 minutes; SD 6.77 and 5.73 minutes; CI (-4.79, 5.85); p=0.838). Visits which had OTDMS downloads contained longer discussions about SMBG (2.33 vs 1.70; SD 1.00 and 0.83; CI (-0.150, 1.410); p=0.108) and BG trends (1.18 vs 0.80; SD 0.70 and 0.35; CI (-0.099, 0.859); p=0.112). Additionally, when OTDMS was used, conversations were more specific and physicians reported greater confidence in recommendations. Physicians reported that OTDMS allowed them "more time educating, less time gathering data" than written records. Patients whose visits utilized OTDMS were more likely to test before appointments, rate their disease as well controlled, and retain SMBG recommendations.

No previous studies have examined how structured data as contained in OTDMS impacts physician-patient discussions. This study suggests more targeted discussions around patterns and trends using SMBG occur when

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OTDMS is used, without significantly increasing total visit lengths. The role that patient factors play in the observed differences is unclear.

OTDMS use may help physicians identify and communicate patterns associated with SMBG. Further study is required to see if enhanced discussions improve clinical outcomes.

2197-PO

Is More Frequent Self-Monitoring of Blood Glucose in Type 2 Diabetes Associated with Improved Metabolic Control?

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The role of self-monitoring of blood glucose (SMBG) in type 2 diabetes treatment remains controversial, and the effect of SMBG on the medication dosage adjustment in type 2 diabetes is unclear. We conducted a multicentre cross-sectional study assessing the relationship between application of SMBG and the glycemic control. The study group comprised 564 patients with type 2 diabetes (mean age [±SD] 64.3±9.9 years, diabetes duration 10.4±8.4 years, BMI 31.3±5.5 kg/m2, 59.7% treated with insulin, HbA1c 7.37±1.26%, fasting and postprandial blood glucose 128±27 and 150±34 mg/dl, respectively). The patients were asked to fill in a standardized questionnaire consisting of closed questions regarding their use of SMBG. Mean frequency of SMBG was 2.9±1.3/day and 18.1±10.2/week. The patients who performed SMBG ≥3 times/day as compared to SMBG <3 times/day had longer duration of diabetes (11.5±9.0 vs 9.2±7.5 years, p<0.01), higher HbA1c (7.63±1.33 vs 7.28±1.10%, p<0.01), were taking insulin more times daily (3.1±1.2 vs 2.4±1.1 injections/day, p<0.001) and were treated with higher daily insulin dose (56±31 vs 44±26 IU, p<0.001). More frequent SMBG showed slight but significant positive correlation with HbA1c (r=0.144, p<0.05) and insulin daily dosage (r=0.229, p<0.05). However, multiple regression analysis showed that only BMI and not frequency of SMBG was a independent determinant of HbA1c.

Patients performed SMBG "to know their blood glucose" (76%), "per doctor's order" (67%), and "to know what to eat" (53%). Antidiabetic medication dosing was modified according to SMBG results by 46% of subjects. Pre-meal elevated blood glucose resulted in food intake decrease in 51%, and increase in physical exercise in 55% of the studied subjects. In conclusion, SMBG does not seem to be associated with improved metabolic control in type 2 diabetes – probably the opposite is true i.e. patients with worse glucose control tend to perform SMBG more often. As only half of subjects change their behavior due to abnormally high results of SMBG, therefore patients with type 2 diabetes should be educated more effectively to utilize SMBG to modify their lifestyle.

2198-PO

Metabolite Profiling of Plasma from T2DM and Healthy Volunteers: Variability Assessment and Metabolic Alterations

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The full biochemical profile in Type 2 diabetes mellitus (T2DM) patients and how it differs from that in healthy individuals has not been fully described. A rich characterization of the differences in metabolite profile between T2DM and healthy volunteers (HV) may lead to the identification of new relevant pathways and potential drug targets, as well as diagnostic and mechanism biomarkers related to T2DM susceptibility and disease progression, and its associated complications.

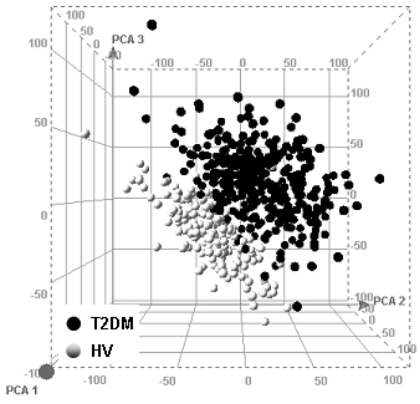
In this study, 205 endogenous metabolites were measured by LC/MS/MRM in 19 T2DM subjects and 11 HV controls. All subjects provided written informed consent. Plasma samples were collected pre and post a standardized meal challenge (Boost High Protein; 7 kcal/kg) following an overnight fast and repeated over 3 consecutive days. The inter- and intra-subject variability for 95% of detected metabolites was < than 55% and 20% respectively. Comparable variability was observed across T2DM and HV groups. Principal component analysis showed differentiation of T2DM from HV profiles (Fig. 1) and separation between fasting and fed states. Analysis of variance revealed changed metabolites in T2DM (Table 1) pointing to several altered metabolic pathways (e.g. carbohydrate & lipid metabolism, neuro-hormonal dysregulation). In conclusion, the LC/MS/MRM based metabolomics assay allows simultaneous detection of multiple T2DM-related markers and serves as a platform for analysis of pathway that may be related to T2DM susceptibility, progression, and treatment response.

Table-1 Significantly Changed Metabolites in T2DM

Metabolite	Intersubject CV (day1 / day2)	Intrasubject CV (day1 / day2)	Effect Size (beta value) (day1 / day2)	p value (day1 / day2)	Adjusted p** (day1 / day2)
Metanephrine	26.0 / 27.1	7.6 / 8.8	-1.315 / -1.368	6.56E-12 / 6.53E-10	<0.0001 / <0.0001
Fructose / Glucose / Galactose	25.2 / 24.7	9.2 / 9.1	-1.223 / -1.358	2.19E-10 / 5.05E-10	<0.0001 / <0.0001
OH-Phenylpyruvate	25.7 / 25.6	9.2 / 8.9	-1.211 / -1.294	6.14E-10 / 7.20E-9	<0.0001 / <0.0001
Fructose / Glucose / Galactose*	26.0 / 23.6	9.3 / 9.5	-1.176 / -1.384	1.08E-9 / 7.61E-11	<0.0001 / <0.0001
Lactose	26.8 / 25.3	8.7 / 9.8	-1.168 / -1.324	2.14E-9 / 2.22E-10	<0.0001 / <0.0001
Carnitine / Mannose	29.2 / 25.9	7.9 / 10.5	-1.264 / -1.41	2.21E-9 / 3.90E-10	<0.0001 / <0.0001
Ascorbate/Dihydroorotate/ (2S)-2-Isopropylmalate	26.1 / 24.6	11.3 / 12.1	-1.012 / -1.068	1.11E-7 / 2.74E-6	0.0002 / 0.001
Acetylcholine	40.0 / 44.5	10.4 / 11.2	-1.393 / -1.284	1.59E-5 / 5.84E-5	0.0032 / 0.0129
3-OH-butyrate / Hydroxypyruvate	39.1 / 42.0	11.0 / 11.6	-1.281 / -1.223	6.21E-5 / 8.70E-5	0.011 / 0.0181
Inositol	24.7 / 25.0	16.1 / 14.3	-0.806 / -0.902	2.19E-4 / 8.38E-5	0.0365 / 0.0178

* measured in the 2nd column ** 10000 permutations

Figure 1 PCA Scores Plot Showing Differentiation of T2DM from HV Group



2199-PO

One to Two Year Follow-Up of Patients with Reported Broken Continuous Glucose Monitor (CGM) Sensor Wires

JESSICA LARRABEE, MICHELLE FOURNEY, DAVID A. PRICE, *San Diego, CA*

A broken and retained sensor wire is a rare occurrence with CGM use, reported with 0.03% of Dexcom SEVEN sensors. Sensors are supplied sterile and applied to clean skin. Accordingly, current recommendations for broken sensor wires are conservative: "If a sensor breaks and no portion of it is visible above the skin, do not attempt to remove it. Seek professional medical help if you have signs of infection or inflammation at the insertion site." Dexcom received 43 complaints from 41 patients about potential broken and retained sensor wires throughout 2009. During December, 2010, Dexcom attempted to contact these patients and surveyed 21 respondents (23 incidents) over the phone about sequelae and current CGM use.

Of the 21 respondents, 19 were moderately to highly confident that the sensor wire broke under their skin. At present, 13 are moderately to highly doubtful the wire is still under their skin while 6 are moderately to highly confident that it is. Four respondents report they saw the wire remove itself from their skin. Four respondents saw a health care professional about the incident and only 1 had a minor procedure performed to extract the wire because of an infection. At the time of the incident, 13 respondents recall little or no discomfort while 3 recall moderate to severe discomfort. At present, no respondent reports any discomfort. Four respondents continue to have moderate or significant concern about the incident today, while 14 have little or no concern. Fifteen respondents report that the incident had little or no affect on CGM usage, 14 are still active CGM users, and 4 report that their incident did affect their ongoing use of CGM. Respondents that are not currently using CGM stopped using for a variety of reasons. No respondent is using another CGM system.

The current recommendation appears appropriate as in this survey, there were no significant deleterious health consequences reported. The majority of respondents do not believe the wire remains under their skin, experienced no discomfort and continue to have no discomfort, have little concern about the incident, did not seek healthcare follow-up, and are still using CGM.

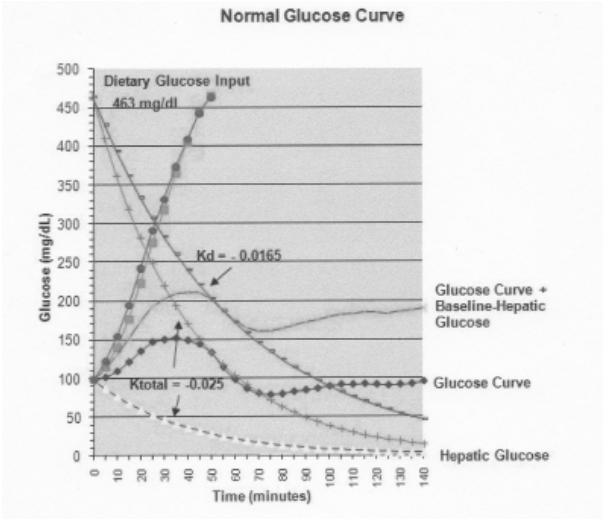
For author disclosure information, see page 785.

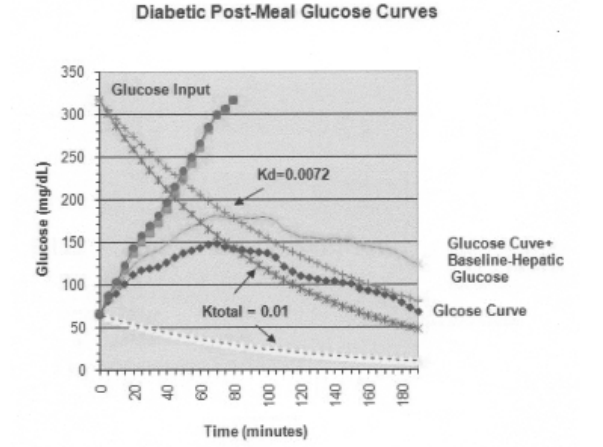
2200-PO

Pharmacokinetic Analysis of Meal-Related Continuous Monitoring Glucose Concentrations

JOHN S. MELISH, *Honolulu, HI*

Continuous Glucose Monitoring (CGM) is successfully used to provide qualitative and statistical summaries to improve diabetic management. Presented here is a minimal model pharmacokinetic evaluation of post-meal glucose concentrations from a normal individual and a Type 2 patient requiring insulin.





It presumes zero order glucose input and first order peripheral glucose disappearance (-Kd). Dieary glucose appearance is approximated by glucose concentrations in time/EXP)-Ktotal*time), where -Ktotal = -Kl-Kd. Kd, Ktotal,Kl are expressed as fraction/minute (1/time). Curves above actual meal-related concentration curves represent dietary glucose replacing deeasing hepatic glucose added on to the inital glucose curve. Diabetic concentration curve analysis vs. non-diabetic curve: Shift of curve peak to the right (delay); higher centration peak; about half the disposal rate; less rapid fall in hepatic glucose; a slower return to baseline. The latter is likely due to an earlier return of hepatic glucose production and a decrease in insulin effect. Using a volume of distribution (Vd) of 0.21 of kg body weight, a dietary glucose clearance can be estimated as well as a splanchnic first pass glucose uptake. This model is compatible with physiologic meal-related glucose disposal. It can be applied directly to carbohydrate/exogenous insulin ratios, glycemic index measurements, and appropriate timing of insulin administration.

2201-PO

Quantification of Urine Glycoproteins for Assessment of Impaired Glucose Tolerance

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Pre-diabetes is defined by the presence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. Recent data suggest that isolated IGT represents ~16% of overall pre-diabetes. IGT, alone or in conjunction with IFG, is associated with a greater risk of conversion to frank diabetes than isolated IFG. IFG and IGT are additionally distinguished by differences in the sites of associated insulin resistance and extent of the beta-cell secretory defect, and may benefit from different therapeutic interventions to halt or delay disease progression. While IFG can be detected with a fingerstick, the standard for determination of IGT is the oral glucose tolerance test (OGTT), which is invasive, time-consuming, and poorly reproducible. We have previously reported increased levels of urinary glycoproteins in diabetic nephropathy, and subsequently extended this analysis to demonstrate elevated levels of urine glycoproteins in pre-diabetes. In this study, we specifically addressed the ability of general and specific glycoprotein biomarkers to detect IGT to evaluate whether a non-invasive urine test would perform similarly to the standard OGTT. A total of 132 Asian-Indian adults provided OGTT measures and second-void fasting urine samples. Participants were categorized using established criteria for diagnosis of IGT (OGTT $\geq$ 140 mg/dl). Total reactivity to various lectins and levels of specific glycoproteins were quantified using ELISA. Among the parameters evaluated, Concanavalin A reactivity and alpha-1 acid glycoprotein levels demonstrated statistically significant age and total protein-adjusted odds ratios (95% CI; p-value) of 1.55 (1.05, 2.28; p=0.03) and 1.37 (1.07, 1.75; p=0.01), respectively. Area under Receiver Operating Characteristic curves (AUCs) illustrated a moderate ability to discriminate between normal glucose tolerance and IGT [AUC (95% CI): 0.66 (0.57, 0.76) and 0.68 (0.59, 0.77), respectively]. These values were not modified by the presence or absence of frank diabetes (n=22). Our results demonstrate that urinary glycoprotein profiles represent a potential simple, non-invasive alternative to standard OGTT as a screening test for IGT.

2202-PO

Ramadan Fasting among Muslim in Type 2 Diabetes: A Comparison between Patients with Good and Poor Glycemic Control Using Continuous Glucose Monitoring (CGM)

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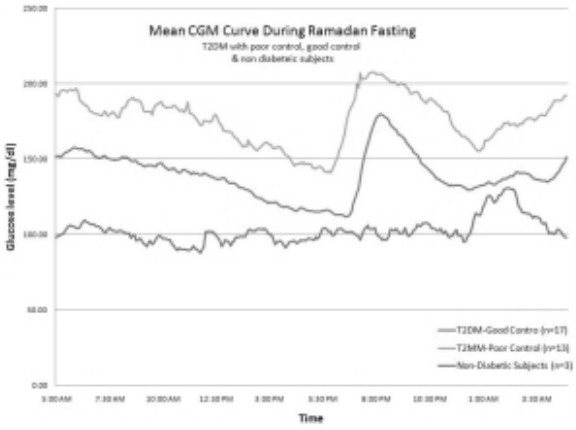
Many Muslim patients with diabetes practice dawn to dusk fasting during the holy month of Ramadan. We have used CGM to explore and compare the changes in glucose profiles among patients with good and poor glycemic control.

Thirteen patients with type 2 diabetes mellitus (T2DM) and poor glycemic control (age 46 ± 8 years, BMI 30.8 ± 4.2 kg/m2) were compared with seventeen patients with T2DM and good glycemic control (age 43 ± 13 years, BMI 27.5 ± 4.1 kg/m2). For each subject CGM was performed for three days before and later during Ramadan fasting. Any change of treatment was at the discretion of the attending physician. CGM during Ramadan fasting period was performed on three non-diabetic volunteers. Mean CGM curves were constructed on each group for Ramadan and non- Ramadan periods.

With Ramadan fasting, mean glucose level increased from 172.2 $\pm$ 17.6 to176 $\pm$ 16.5 mg/dl in poorly controlled group ($p< 0.0001$) and from 135.3 $\pm$ 5.7 to 139.3 $\pm$ 15.3 mg/dl in well controlled group ($p<0001$). During Ramadan fasting period CGM curves in both well controlled and poorly controlled patients showed a characteristic rapid rise in blood sugar at Iftar (breaking of the fast) time. The magnitude of this rise was higher in the poorly controlled patients. There was a highly significant difference in mean glucose level between the two groups which persisted during Ramadan fasting.

For author disclosure information, see page 785.



Minor overall deterioration in glycemic control occured among diabetic patients. In both groups glycemic control average glucose was lower between sunrise and sunset and higher after sunset. Patients with diabetes should need to have adequate control before deciding to fast during Ramadan. Nutritional advice should include reducing high glycemic index food during Iftar.

Supported by: Sheikh Hamdan Award for Medical Sciences

2203-PO

Reduction in Glycated Albumin Can Predict Change in Hemoglobin A1c: Comparison of Oral Hypoglycemic Agent and Insulin Treatments

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Aim: To investigate whether the percent change in glycated albumin (GA) 3 weeks after initiating anti-diabetes treatment could predict the corresponding change in glycated hemoglobin (A1c) 3 months later.

Methods: 140 patients were enrolled into two groups: group I (insulin-based; n = 100) and group II (OHA-based; n = 40). Both GA and A1c levels were measured during hospitalization. GA was measured again at 3 weeks (1st visit) after the initial measurement and A1c was measured at 3 months (2nd visit). The percent change in GI was defined as 100 × (follow-up GI – hospital GI)/ hospital GI.

Results: In both groups, the percent change in GA at the 1st visit and in A1c at the 2nd visit showed a moderate linear relationship (r = 0.735; p < 0.01). Group II (r= 0.778; p < 0.01) demonstrated a slightly stronger linear relationship than group I (r = 0.738; p < 0.001); however, there was no statistically significant difference between the two groups.

	Percent change in GA (%) after 3 weeks	Percent change in GA (%) between 1st and 2nd visit	Percent change in GA (%) after 3 months	Percent change in A1c (%) after 3 months
All (n=140)	19.12 ± 14.41	10.05 ± 21.89	23.3 ± 20.5	22.09 ± 14.69
Group I (insulin-based, n=100)	18.56 ± 13.87	12.34 ± 20.23	28.28 ± 21.11	23.09 ± 14.87
Group II (OHA-based, n=40)	20.54 ± 15.77	4.32 ± 24.96	24.99 ± 19.00	19.56 ± 14.12
p-value	0.464	0.056	0.405	0.200

p-value by *t*-test, group I vs. group II
Data expressed as frequencies (%), or means ± SD.

A correlation between the percent change in GA and A1c was not affected by sex, age, body mass index, hemoglobin, serum creatinine, or albumin.

Conclusion: The percent reduction in GA 3 weeks after the initiation of treatment corresponded with the reduction in A1c 3 months after starting treatment in both OHA- and insulin-treated Korean type 2 diabetic patients.

Table 1. Clinical characteristics of study subjects.

	All (n=140)	Group I (insulin based, n=100)	Group II (OHA based, n=40)
Age (years)	57.29 ± 12.23	57.08 ± 11.97	57.80 ± 13.01
Male (%)	79 (56.43%)	55 (55%)	24 (60%)
BMI (Kg/m^2)	24.38 ± 3.69	23.95 ± 3.41	25.49 ± 4.19
Hemoglobin (mg/dL)	13.92 ± 1.64	13.67 ± 1.54	14.50 ± 1.74
S-creatinine (mg/dL)	1.00 ± 0.88	0.93 ± 0.25	1.17 ± 1.59
S-albumin (g/dL)	4.46 ± 0.48	4.44 ± 0.49	4.50 ± 0.46
FPG (mg/dL)	164.27 ± 53.58	170.52 ± 57.92	151.25 ± 40.89
PPG (mg/dL)	271.96 ± 80.32	283.69 ± 83.22	246.83 ± 68.23
A1c (%)	9.37 ± 2.01	9.81 ± 2.00	8.29 ± 1.60***
GA (%)	27.01 ± 10.26	28.97 ± 10.80	22.13 ± 6.71***
Insulin, fasting (μIU/mL)	11.46 ± 11.87	11.64 ± 12.89	11.02 ± 9.04
Insulin, postprandial (μIU/mL)	41.23 ± 28.13	35.95 ± 23.07	54.86 ± 33.92**
C-peptide, fasting (ng/mL)	2.92 ± 3.30	2.65 ± 2.52	2.84 ± 1.82
C-peptide, postprandial (ng/mL)	4.48 ± 2.68	3.85 ± 2.40	6.06 ± 2.71***
HOMA-IR	4.15 ± 4.57	4.41 ± 5.25	3.62 ± 2.74
Insulinogenic index	0.17 ± 2.09	-0.07 ± 2.29	0.68 ± 1.45

Data expressed as frequencies (%), or means ± S.D. The means of data between Group I and Group II were compared using paired t-test BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; A1c, glycated hemoglobin(HbA1c); GA, glycated albumin.

HOMA-IR= [basal insulin (μIU/mL) × glucose (mmol/L)]/22.5, insulinogenic index(IGI)=[insulin(90′) – insulin(0′)]/[glucose (90′) – glucose (0′)]

*** p < 0.001 Group I vs. Group II by *t*-test ** p<0.01 Group I vs. Group II by *t*-test

2204-PO

WITHDRAWN

2205-PO

The Relationship between Glycemic Variability and Macrovascular and Microvascular Complications in Type 2 Diabetes

YU LIU, YANGYANG LI, HAIQIN CAI, XIUJUAN ZHANG, *Changchun, China*

It is debated whether glycemic variability may confer a risk of microvascular and macrovascular complications that is in addition to the mean blood glucose (MBG) value alone. This study monitoring the continuous glucose level to assess the effect of glucose variability on the risk of macrovascular and microvascular complications in type 2 diabetes. 59 inpatients with type 2 diabetes mellitus underwent 72-hour glucose monitoring, they are divided into three groups based on index of blood glucose variability, including less variability group (index<1.5, A group), mild variability ((index>1.5~3.0, B group) and severe variability group ((index>3.0, C group). In each group glycosylated hemoglobin(HbA1C), urinary micro albumin(MA), fasting blood glucose (FBG), fasting plasma insulin (INS), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL - C), low-density lipoprotein bile, blood uric acid (UA) were assayed. The age, duration of diabetes, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, coronary heart disease and stroke history were recorded. The fundus oculi, ankle brachial index (ABI) and carotid artery ultrasound were measured. The results show that the positive rates of urinary micro albumin in three groups were 31.6%, 45.5% and 66.7% respectively, while the positive rate of retinopathy complication were 10.5%, 18.2% and 33.3% respectively. The prevalence of micro vascular complications in group C was significantly higher than those in group A and group B (P <0.05). Carotid artery intima thickness in three groups was 21.1%, 22.7%, and 22.2% respectively. Carotid artery plaque were found in 31.6% patients of group A, 31.8% in group B, and 26.3% in group C. 5.3%, 9.1%,

For author disclosure information, see page 785.

and 5.6% patients in each group were found to have the decrease of ABI while there were not significant differences among these three groups. We could get a preliminary conclusion that blood glucose variability is important predictors in diabetic microvascular complications which are independent of glycosylated hemoglobin.

Supported by: The Fok Ying-Tong Education Foundation of China (No.111041)

2206-PO

Towards a Truly Non-Invasive Glucose Monitor—Progressive Stages

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Non-Invasive (NI) tracking of physiological phenomena correlated with Blood Glucose (BG), using a single methodology, encountered obstacles of non-specificity, since factors, other than glucose influence tissue parameters as well and cause inaccuracies in the reading. An alternative approach using a combination of 3 NI methods: ultrasonic, electromagnetic and thermal has been proposed. The weighted average reading reflects the BG value with smaller impact of interferences, leading to more accurate results. GlucoTrack® comprises a Main Unit and 3 different sensor pairs, located at the tip of a Personal Ear Clip (PEC). The development of such a device is complex and contains several stages, essential to reach reliable and robust utility.

Clinical trials were initially launched in the clinic and followed by home trials. Subsequent to 2007 trials, conformational changes in the sensors, together with mechanical PEC re-design were implemented, ensuring consistent pressure and better contact. Environmental factors, such as ambient temperature, were addressed following 2008 trials, mainly by updating the data processing algorithm. 2009 trials led to the addition of a new temperature sensor, located in a more inert location, as well as fine-tuning of the data processing algorithm. The implemented changes were tested in initial home trials during 2010. Further home trials (in 2011) will evaluate the upgraded device performances and ease of operation in real home environment, and will re-confirm calibration validity for a period of at least one month.

The following table depicts the progress in results' reliability:

			Clarke Error Grid Results	
Trials	Subjects	Mean ARD (%)	A zone (%)	A+B zones (%)
Clinic: 2007	135	29.9	50	92
Clinic: 2008	42	23.6	58	97
Clinic: 2009	61	21.9	61	97
Home: 2010	8	25.7	55	95

A positive progress trend in the results' accuracy can be clearly observed throughout the developmental process. Furthermore, the initial home trials show no significant degradation relative to the results obtained in the clinic. The long intervals between re-calibrations, the ability to perform frequent spot measurements and acceptable accuracy, present high likelihood for a solution to improve BG monitoring adherence.

2207-PO

Usage and Usefulness of a Blood Glucose Meter Device Reader and Diabetes Management Tool (Accu-Chek® Smart Pix) in the Management of Type 2 Diabetes Mellitus in Primary Care

CARLOS BROTONS, MARIA-JOSÉ COMELLAS, TRANSFER STUDY GROUP, *Barcelona, Spain, Sant Cugat del Vallès, Spain*

Good control of glucose is important in preventing and delaying the complications of type 2 diabetes mellitus (T2DM). We designed an observational, prospective and multicenter study to assess the usefulness of a blood glucose meter device reader(Accu-Chek® Smart Pix), a device that visualises and analyses blood glucose values, in the management of the T2DM patients in primary care settings. Nurses' satisfaction with the device and the attitude change of the patients towards the management of the T2DM disease were assessed by a questionnaire (5-point Likert scale). Changes in glycosilated haemoglobin (HbA1c) and changes of blood glucose levels after an observational period of 6 months were also evaluated. Data was obtained from 223 patients recruited in 32 primary care centers in Spain. Our results showed a significant HbA1c level reduction from 8,92 % at baseline to 8,04 % after 6 months ($p<0.001$), and an increase in the proportion of patients with blood glucose levels below 7,5% from 22,7% at the beginning to 31,4% at the end of the study. In 91% of patients, nurses considered the device as very useful/useful in the management of T2DM patients. In these patients, the device was seen as beneficial for patient-nurse communication (85%), visualization of glucose levels (78%), and therapeutic decision making (63%). In almost all cases, nurses considered the device easy to use, secure for disease management, fast and clear in the acquisition of data, and positive in the interaction with patient. A significant increase in patients' comprehension, motivation, attitude, and satisfaction towards the management of the disease was observed at the end of the study. In addition, a significant increase in the proportion of patients who controlled blood glucose before waking-up, before and after having breakfast, after having dinner, and before going to bed, was detected. In conclusion, our results demonstrate the usefulness of this device in managing patients with T2DM in primary care, and the subsequent benefits in the control of HbA1c and blood glucose levels in these patients.

2208-PO

Variability in Comparison of HbA_{1c} Levels with Self-Monitored Mean Blood Glucose Levels in Type 1 Diabetic Patients

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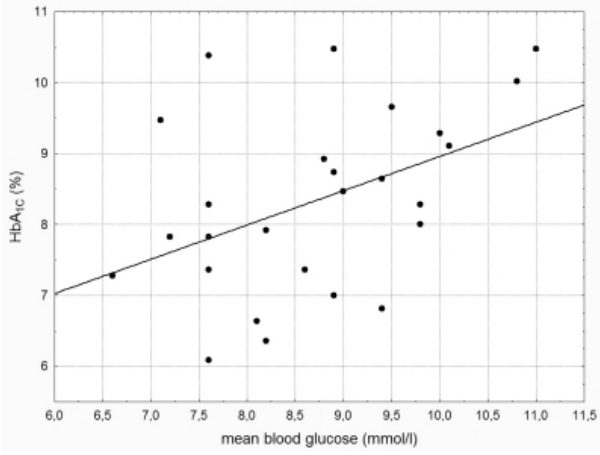
Aims: HbA_{1C} is a well established parameter used for the assesment of diabetes control. HbA_{1C} was recommended by the ADA also for the diagnosis of diabetes. The aim of the study was to compare HbA_{1C} with mean blood glucose (MBG) in T1DM patients and to look for interindividual variability of HbA_{1C}.

Patients and methods: Twenty-seven T1DM patients (mean age 44±14 years, mean HbA_{1C} 8.4 ± 1.3 %) were included in the study. They performed SMBG on a regular basis in their usual manner. SMBG data measured in a 12-weeks period were downloaded from their personal blood glucose meters and MBG was calculated. HbA_{1C} was measured by HPLC on a Variant II BioRad analyzer in one laboratory using IFCC calibration. Results were calculated by standard statistical methods, data are mean ± SD.

Results: The average number of glucose measurements was 145 ± 68 (range 38 – 386), average count of glucose measurements per day was 2.4 ± 1.5 (range 0.6 – 6.3). A linear Pearson correlation between MBG and HbA_{1C} was calculated: $HbA_{1C} = 4.13 + 0.48*MBG$ ($r = 0.44$, $p = 0.025$). This relationship is shown in the figure.



Significant differences in HbA_{1C} levels were observed between patients with similar MBG calculated from the results of SMBG (e.g. for MBG = 7.6 mmol/l different values of HbA_{1C} have been observed in four different patients: 6.1, 7.4, 7.8 and 10.4% according to IFCC). Similarly large variation of MBG was found for one HbA_{1C} level.

Conclusions: HbA_{1C} can be used as an important parameter of the long-term diabetes control, especially when evaluated in the follow-up of an individual patient. Although there can be some bias in the SMBG values our data demonstrate large variation of HbA_{1C}. It should be taken into an account when HbA_{1C} values alone would be used for the diagnosis of diabetes.

Supported by: Research Project MSM0021620807

2209-PO

WITHDRAWN

For author disclosure information, see page 785.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—INSULIN DELIVERY SYSTEMS

2210-PO

1 Year Metabolic Evolution in Type 2 Diabetes Patients Treated by Subcutaneous Ambulatory Insulin Pump

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Can insulin pump therapy be a response to the failure of an optimized multi injection insulin treatment on type II diabetes (D2) patient and in which conditions?

172 D2 patients switched to an ambulatory s/c insulin pump therapy from insulin multi-injections (3 ± 0.7/day with metabolic failure/HbA1C: 9.1 ± 1.8 %).

A follow up is run after 1 year (T_1Y) for 96 patients (55.8%) went on with the pump. 8 patients stop the treatment.

- HbA1C decreases by 1.4 ± 1.9% (from 9.0 ± 1.8% -T0 to 7.6 ± 1.4%- T_1Y) with 35 (43%) patients <7.5%, 40 (56%) with a decrease ≥1% and according to the HbA1C baseline tertiles : <8% (N=21) = -0.2 ± 1.1%, >8<9.5 % (N=27) = -0.9 ± 1.0%, >9.5% (N=24) = -3.0 ± 2.0%.

- Weight increase by 3.5 ± 5.4 kg (from 94 ± 18.1 - T_0 to 97.5± 18.5 kg T_1Y), with 15 patients <2kg, 27 patients >5kg and according to the initial BMI tertiles (m2/kg): <30 (N=15): +1.7 ± 1.5 kg, >30<35 (N=27): +0.7 ± 1.7 kg and >35 (N=26): +1.2 ± 4.3 kg. There is no significant Hba1C decrease according to these BMI levels: -1.6 ± 2.0%, -1.2 ± 1.6% and -1.6 ± 2.1%.

- The average insulin dose decrease by 0.23 ± 0.3 U/kg/day (from 1.13 ± 0.6-T_0 to 0.90 ± 0.3-T_1Y),with 9 patients <0.5 U/kg/day, 49 >1U/kg/day and according to the initial insulin dose (U/kg/day) tertiles: <0.8 (N=19): +0.17 ± 0.2, >0.8<1.2 (N=27): -0.16 ± 0.3, >1.2 (N=22): -0.59 ± 0.5

12 severe hypoglycaemias (4patients) have been noticed at T_0, none after 1 year.

We have compared "good responders" (defined by HbA1C decrease T_1Y ≥ 10 %/T_0), versus "bad responders" (<10%) and we have no found any difference (T_0) for age, BMI, insulin dose but for T_0 HbA1C levels (9,8±1,9 vs 7,9±1,2 %-p<0,001) and so for the evolution T_0- T_1Y : -2.4 ± 1.7% vs +0.1 ± 0.9%- p<0.0001 while weight (+4.5 ± 5.5 vs +3.1 ± 5.4 kg) and insulin dose (-0.18 ± 0.47 vs -0.23 ± 0.35 U/kg/d) evolution are no significant.

Conclusion: Using subcutaneous ambulatory pump, after failure of multi-injections, allows a real metabolic improvement, without excessive weight gain, with a decrease in insulin needs and no major hypoglycaemia. The results appear to be more satisfactory when baseline HbA1c (≥ 8%) and starting insulin doses (≥ 0.8 u/kg/d) are higher.

2211-PO

A Novel Strategy for Non-Empirical Calculation of Prandial Insulin Bolus Based on Continuous Glucose Monitoring (CGM) in Subjects with Type 1 Diabetes (T1DM) Treated with Continuous Subcutaneous Insulin Infusion (CSII)

PAOLO ROSSETTI, F. JAVIER AMPUDIA-BLASCO, ALEJANDRO LAGUNA, ANA REVERT, JOSEP VEHÍ, REMEI CALM, JUAN F. ASCASO, JORGE BONDÍA, *Valencia, Spain, Girona, Spain*

Success with CSII is highly dependent on the patients' and physicians' skills, being prandial insulin dosing (traditional bolus - *tBolus*) an empirical practice. Here a non-heuristic method for prandial insulin administration (set-inversion bolus - *iBolus*), is presented along with preliminary results of its clinical validation in T1DM patients.

An individual patient's model characterizing a 5-hour postprandial period (0-5h PP) was obtained from a 6-day CGM period. A model with interval parameters accounting for patient variability was calculated considering 20% uncertainty in insulin sensitivity and 10% in carbohydrates (CHO) estimation. Based on this model, constraints on plasma glucose (PG) were posed and a set-inversion problem let to a set of solutions (the *iBolus*) that contained a bolus insulin dose, a specific mealtime basal insulin dose and the time for restoration of basal to baseline values.

To validate the *iBolus,* a double-blind, crossover study is being performed where each patient undergoes 4 meal tests with 40 g or 100 g CHO in two occasions, respectively. In each meal, the *iBolus* was compared with the *tBolus,* given in random order before the meal (t0). A previous insulin feedback was performed to standardize PG_{t0}. Intravenous glucose infusion (GI) was started during the 0-5h PP if necessary to avoid hypoglycemia.

Seven out of 12 T1DM patients on CSII (4F/3M, mean±SD, age 40±7.7 y, BMI 26±2.4 kg/m^2) have completed the study. After the meal, the area under the curve (AUC) of PG above 140 mg/dl during the first 2h (AUC-PG_{0-2h}) and the AUC–GI_{0-5h} were not different with either bolus for 40g CHO (*iBolus* vs *tBolus,* 22±33 vs 22±31 mg/dl·h and 170±145 vs 35±75 mg/kg, respectively) or 100 g CHO meals (23±31 vs 13±14 mg/dl·h and 18±33 vs 40±96 mg/kg). In conclusion, our study shows that the *iBolus* has at least a similar efficacy and hypoglycemic risk as the *tBolus* (p>0.05, ANOVA). If confirmed, these data indicate that a CGM based, user-independent algorithm for prandial insulin administration is feasible in T1DM patients using CSII therapy.

2212-PO

Comparison of HumaPen® Luxura™ HD and NovoPen® Junior for Overall Ease of Use

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Insulin pens deliver accurate, precise doses of insulin, important for children who often require low doses and are at risk for hypoglycemia. Two reusable insulin pens that can deliver insulin in ½U increments are HumaPen® Luxura™ HD (½ to 30U) and NovoPen® Junior (1 to 35U). This randomized, 1-day, open-label, multicenter, 2-period, crossover study compared the ease of use of these 2 devices in 65 adult caregivers of children aged 3-12 yr with type 1 diabetes. Caregivers had to have ≥6 mo experience giving insulin to a child and no prior experience with either device. Each caregiver had to change the cartridge, dial and correct the dose, and inject into an injection pad at a high dose (10U corrected to 6.5U) and a low dose (5U corrected to 2.5U). After testing each insulin pen at each dose, each caregiver completed a 9-item questionnaire (8 items were derived from a cognitively debriefed item pool) scoring the pens' attributes on a 7-point scale (1=strongly disagree; 7=strongly agree), and a final preference question. The 4 combined scores from the questionnaires for each caregiver were used to assess the primary endpoint (overall ease of use) and secondary endpoints (ease of changing cartridges and ease of correcting dose). Caregivers with no preference (equal combined scores for each device) were excluded from the analyses (table).

Endpoint	Caregivers Preferring HumaPen Luxura HD n (%)	Caregivers Preferring NovoPen Junior n (%)	Exact 95% CI for Binomial Proportion (of caregivers with a preference)	No Preference n (%) of total N=65
Overall Ease of Use	36 (94.7%)	2 (5.3%)	82.3%-99.4%	27 (41.5%)
Ease of Changing Cartridges	32 (94.1%)	2 (5.9%)	80.3%-99.3%	31 (47.7%)
Ease of Correcting Dose	47 (94.0%)	3 (6.0%)	83.5%-98.7%	15 (23.1%)

The lower CI limit of the proportion of caregivers with a preference who preferred HumaPen Luxura HD was ≥50%. Differences between groups were statistically significant. For the final preference question, 52 (80.0%) of the 65 caregivers preferred HumaPen Luxura HD over NovoPen Junior,

For author disclosure information, see page 785.

confirming that HumaPen Luxura HD is an easy-to-use insulin pen preferred by adult caregivers for giving insulin to children with type 1 diabetes.

Supported by: Eli Lilly and Company

2213-PO

Doppler Echocardiography in Patients with Type 1 Diabetes Treated with Technosphere® Insulin

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Technosphere Insulin (TI [Afrezza®]) is an ultra rapid acting dry powder formulation of regular human insulin. When inhaled, the time-action profile of TI closely approximates the physiological early phase insulin release. The goal of this substudy was to examine the effects of TI therapy on cardiac function, specifically right heart dynamics (right ventricular systolic pressure [RVSP], RV size and function), in patients with type 1 diabetes.

Doppler echocardiograms (ECHOs) were obtained at baseline and at the final visit (week 16) in a subset of type 1 diabetes patients who participated in a controlled phase 3 study. Patients were randomized to 16 weeks of TI+insulin glargine or insulin lispro+glargine. ECHOs were obtained only at the qualified ECHO labs and reviewed centrally by an independent, blinded ECHO core lab (Cleveland Clinic). RVSP was estimated using the modified Bernoulli equation.

Eighty-nine of 130 patients in the parent trial (40 in the TI group, 49 in the comparator group) participated in the ECHO study. Baseline cardiac function was comparable between the 2 treatment groups (table). After 16 weeks of treatment, no clinically meaningful changes from baseline in any of the ECHO parameters were noted in either treatment group. In addition, RV size and function remained unchanged after 16 weeks of therapy.

Change from Baseline in Echocardiography Measurements

		TI (n=40)	Insulin Lispro (n=49)	
Parameter	Baseline	Change from Baseline	Baseline	Change from Baseline
Ejection fraction (%), mean (SD)	58.8 (3.01)	-0.4 (1.79)	59.1 (3.22)	-0.5 (3.02)
RA pressure (mmHg), mean (SD)	6.1 (2.12)	-0.3 (2.0)	6.0 (2.25)	-0.2 (2.12)
PA diameter (cm), mean (SD)	2.09 (0.31)	0.04 (0.27)	2.06 (0.368)	0.01 (0.32)
RVSP (mmHg), mean (SD)	25.02 (6.66)	1.66 (4.98)	26.60 (6.05)	-1.24 (3.22)
RVEDD (cm), mean (SD)	3.36 (0.48)	0.05 (0.46)	3.27 (0.54)	0.07 (0.46)
RVESD (cm), mean (SD)	2.51 (0.54)	0.03 (0.52)	2.39 (0.51)	0.03 (0.40)

In patients with type 1 diabetes, cardiac function, as assessed by ECHO, remained normal after 16 weeks of TI therapy. Changes in echocardiography parameters were minimal and unlikely to be clinically meaningful.

Supported by: MannKind Corporation

2214-PO

ECLIA or RIA for Insulin Analysis in Pharmacokinetic and Bioequivalence Trials?

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The electrochemical luminescence immunoassay (ECLIA) is a clinical quantitative assay that has the master standard curve for human serum insulin established by the manufacturer. Information for conversion of detector signal to concentration is supplied to the analytical site as a reagent lot-specific bar code along with the dual calibrators run daily; there is no longer a need to "run" a standard curve with each analytical run. As such, the assay deviates from the FDA's Guidance for Industry: Bioanalytical Method Validation, raising the question: Should any deviation from this Guidance exclude an assay from regulatory acceptance as a bioanalytical methodology for a clinical pharmacokinetic or bioequivalence study? While science always precedes a Guidance, when is it possible to use the science before the reissuance of an FDA Guidance?

To confirm the quality of the ECLIA, serum samples (n=1,913) from a bioequivalence study were analyzed for human insulin concentration first using the Roche E170 ECLIA and then a Guidance-conforming radioimmunoassay (RIA; Millipore). Comparing only samples that did not require dilution in the RIA (<160 μU/mL, n=1,412) showed good agreement (R^2=0.92) and a small upward bias (~11%) for the RIA. Incurred sample reanalysis (ISR) further confirmed the consistency of the ECLIA over the RIA methodology (table).

Number (%) of Samples Outside the Specified Window on ISR for the ECLIA and RIA Methods

Assay	>10% Difference	>15% Difference	>20% Difference	>30% Difference
ECLIA (N=218)	8 (3.7)	3 (1.3)	0	0
RIA (N=213)	125 (58.7)	90 (42.2)	63 (29.6)	32 (15.0)

The clinical ECLIA used in this study provided equivalent insulin concentration data to the standard RIA, with a lower limit of quantification (>300 fewer BQL samples with the ECLIA) and a larger dynamic analysis range without dilution. It also demonstrated tighter agreement within ISR. The science indicates that the clinical ECLIA is superior for use for quantification of human serum insulin concentrations in human pharmacokinetic and bioequivalence studies, even though the calibration curve is not actually "generated in each analytical run."

Supported by: MannKind Corporation

2215-PO

WITHDRAWN

2216-PO

Good Glycemic Control Is Positively Associated with the Levels of Serum Albumin and Postprandial C-Peptide after Long-Term Continuous Subcutaneous Insulin Infusion Treatment in Patients with Type 2 Diabetes

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To investigate association factors other than plasma glucose in relation to achieving optimal A1C level after long-term continuous subcutaneous insulin infusion (CSII) therapy in type 2 diabetic patients who had been poorly controlled, we analyzed the clinico-laboratory data of the patients treated with CSII therapy for 6-12 months at Konkuk University Diabetes Center between June 2004 and March 2007: inclusion criteria for the study were A1C level ≥7.0% and serum creatinine ≤1.5 mg/dl at baseline (number 358; male 49%; age 58.8±11.5 yrs; disease duration 12.2±7.8 yrs). The blood samples examined were collected at 12 h-overnight fasting and 2 h after a meal with at least 9 h-cessation of CSII. The mean A1C during the period of CSII therapy (M_A1C) decreased by 6.91±1.18% from 9.30±1.87% at baseline (p<0.0001). The M_A1C was associated positively with the mean A1C at baseline and the fasting M_plasma glucose, and negatively with the M_serum albumin (M_Alb) and postprandial M_C-peptide (M_C_PC) but not with the fasting M_C-peptide after adjusting for age, gender, and M_BMI (p<0.001). In consistent with these results, the proportions of the subjects by the level of the M_A1C or M_Alb changed after CSII therapy (Fig.1A,B) and the M_A1C in subgroups stratified by the M_C_PC or M_Alb value showed significant difference among the groups (Fig.1C,D). In conclusion, our study revealed the achievement of good glycemic control via long-term CSII therapy is associated with factors other than plasma glucose, suggesting that the residual capacity of the postprandial endogenous insulin secretion and the nutritional state represented by serum albumin may play important roles in obtaining euglycemia with CSII therapy.

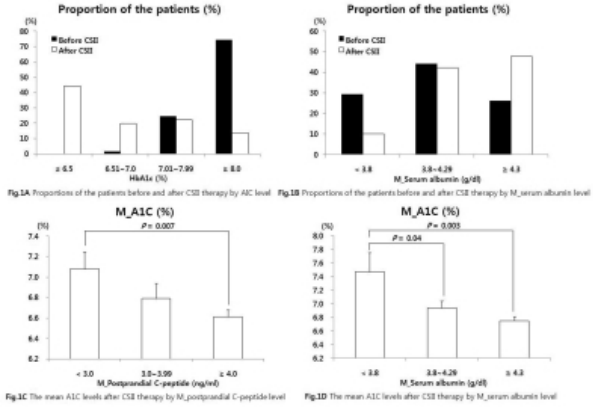

Fig.1A Proportions of the patients before and after CSII therapy by A1C level. Fig.1B Proportions of the patients before and after CSII therapy by M_serum albumin level

Fig.1C The mean A1C levels after CSII therapy by M_postprandial C-peptide level. Fig.1D The mean A1C levels after CSII therapy by M_serum albumin level

Supported by: Novo Nordisk

For author disclosure information, see page 785.

2217-PO

Insulin Pump Therapy May Be Equally Effective in Elderly and Young T1DM Patients

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It is widely accepted that in type 1 diabetes (T1DM) continuous subcutaneous insulin infusion (CSII) via a personal pump is more effective than the multiple daily injections (MDI) model. However, it is not clear whether all age groups of adult T1DM patients may equally benefit from CSII therapy. Especially, the effectiveness of this new technology-based therapy in elderly patients may be of concern.

We aimed to compare the glycemic control and use of selected pump tools in T1DM patients on CSII over the age of 50 (50+ T1DM) with younger subjects.

The last available insulin pump/blood glucose meter downloads and last available HbA1c level of 102 adult T1DM subjects on CSII treatment (mean time duration on CSII: 7.23 years, range 1-13 years) were reviewed. We have divided our population into 2 subgroups: 50+T1DM patients (n=92, mean age: 57.3±7.16 years, duration of diabetes: 24.11±8.05 years, duration on CSII: 6.01±4.19 years) and younger individuals: (n=10, age: 26.39±7.71 years, duration of diabetes: 12.41±7.1 years, duration on CSII 3.93±2.75 years).

There were no differences in glycemic control achieved with CSII treatment by 50+ T1DM patients vs. younger subjects: the HbA1c levels were 6.98±1.04% and 7.13±1.16% (p=0.67), the mean glycemia based on glucometer downloads was 139±29 mg/dL and 142±36mg/dL (p=0.55), respectively. Interestingly, there were no differences with respect to the use of important personal pump options and tools such as daily number of boluses, basal/bolus ratio, frequency of usage of dual-wave/square bolus function and Bolus Wizard option, and continuous glucose monitoring use. 50+ T1DM individuals required more insulin per kilogram (0.71j/kg vs. 0.56j/kg for older and younger individuals, respectively, p=0.036).

In conclusion, insulin pump therapy can be equally effective in T1DM patients older than 50 and in younger adult subjects with this disease.

2218-PO

Patient Satisfaction with the SoloStar® Insulin Pen Device in Medical Practice in Mexico: The LANSOLEAP Study

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The primary objective of the LANSOLEAP study was to evaluate satisfaction with the SoloSTAR® insulin pen by adult patients (pts) with diabetes in Mexico; the secondary objective was to record insulin doses injected per day and evaluate the safety of SoloSTAR.

This was a multicenter, prospective, 1-arm, 6- to 8-week, observational study. Adults with type 1 or type 2 diabetes mellitus (T2DM) who were either insulin users or insulin naïve and taking oral medications and considered to be a candidate for insulin therapy were eligible. Patient satisfaction was evaluated by a self-assessment questionnaire pertaining to overall acceptance (rating of SoloSTAR) and ease and continuation of use. In a second questionnaire, insulin users assessed their preference for SoloSTAR versus their previous device.

A total of 206 patients were enrolled, but 56 were excluded for failing to meet the minimum time of 30 days between visits. Mean age of 150 analyzable pts was 53.3 years (range 18–90 yrs); 58.7% were female, 86.6% had T2DM, 68% had a BMI >25, and 70% previously used insulin. The 7 pts who did not inject insulin themselves were excluded from the satisfaction evaluation. Of the 143 pts who used SoloSTAR, 83.3% rated it as excellent, 15.4% as good and 1.4 % as acceptable; 97% planned to continue its use and 99.3% would recommend it. When insulin users were asked to compare SoloSTAR with a previous device, 78.4% found SoloSTAR easier to use overall; 77.0% found it easier to inject insulin with SoloSTAR. In general, 86.7% preferred SoloSTAR over their previous device. Of pts who had never used a device (n = 56), 83.2% felt confident about using the pen on the same day they received it. After 6 to 8 weeks, 72.7% of pts were injecting 0–30 IU/d with SoloSTAR; 22%, 31–60 IU/d; 0.7%, >61 IU/d, and 4.7% were not using the device. For all 206 pts, there were no adverse events or serious adverse events or any technical complaints reported.

In conclusion, there was a high degree of satisfaction reported with the SoloSTAR pen device among pts in Mexico who had used another device for insulin injections, as well as among first-time insulin users.

Supported by: sanofi-aventis

2219-PO

Pharmacokinetic and Pharmacodynamic Properties of Modified Linjeta™ Formulations in Diabetic Miniature Swine

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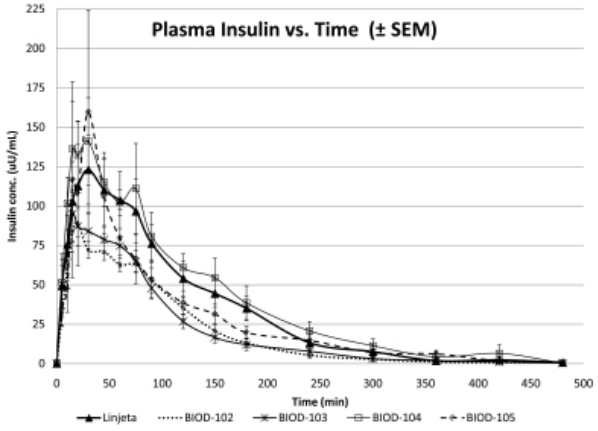
Linjeta™ is a formulation of recombinant human insulin (RHI), disodium EDTA (EDTA) and citric acid (CA), which has an ultra-rapid onset of action in man when compared to RHI or insulin lispro. Previous clinical studies have shown an association with local injection site discomfort following subcutaneous (sc) administration of Linjeta. The aim of the present study was to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) properties of several modified Linjeta formulations predicted to be associated with improved toleration. Six to eight miniature diabetic swine were given a sc dose of 0.25 U/kg Linjeta or the modified formulations, BIOD-102, BIOD-103, BIOD-104 and BIOD-105. Modifications included substitution of EDTA with calcium EDTA (CaEDTA), blending CaEDTA with a reduced concentration of EDTA and increasing the concentration of CA with CaEDTA. Immediately following dosing, the swine were fed 500 g of their normal diet. Blood glucose and plasma insulin were sampled at multiple timepoints from -30 to 480 min post dose. Plasma insulin was measured by an ELISA method and plasma glucose was determined using a YSI glucose measurement. Plasma insulin vs. time is shown in figure below. Changes in glucose concentrations were consistent with the PK, confirming that the new formulations have comparable PK and PD profiles to the original Linjeta formulation. BIOD-102 and BIOD-103 were also evaluated in a clinical study and demonstrated to have significantly improved injection site tolerability and PK profiles in man comparable to those seen in swine (see F. Flacke *et al.*). These data validate diabetic swine as a predictive model for insulin profiles in man and demonstrate the promise of developing insulin formulations that maintain ultra-rapid absorption profiles comparable to Linjeta with significantly improved injection site discomfort.



2220-PO

Progress on a Method of Insulin Pump Control Using Fuzzy Logic

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Type 1 diabetes places many burdens on patients and has significant risk of complications. The development of an artificial pancreas has become more plausible with insulin pumps and continuous glucose monitoring. The University of Virginia has developed an "in silico" simulator for the testing of different controller algorithms. We used this to test our Fuzzy Logic based controller using a simulated 24-hour day. The initial blood sugar was 200 mg/dL. The goal was to test the correction of that blood sugar, control diurnal variations and then evaluate the controller's performance controlling the blood sugar for 30 gram and 60 grams of carbohydrate at 12 & 18 hrs respectively. This was done for a pre-IDE submission

The FL-calculated dose uses current glucose, slope and acceleration/deceleration. The FL dosing matrix design, which remains fixed during operation, reduces insulin dose stacking. Hypoglycemia is further prevented by the use of a Personalization Factor (PF) that uses a linear scaling of the FL dose. The PF takes on integer values between 1 and 8. The higher the PF, the lower the insulin dose. The PF scale factor is a function only of TDD, and remains fixed during controller operation.

The Jaeb 100 in silico adult patient data is summarized in the table below. BG Density is the average percent time in the designated blood glucose range for all patients. CGVA is the percent of patients whose 95% lower and

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95% upper confidence bounds of blood sugars fall within zones A to E, with A and B zones being acceptable.

Personalization Factor	BG Density			CGVA Graph Summary of Patients			
	BG<70 mg/dL	70<180	BG>180	Zone A	Zone B	Zone C	Zones D / E
2	2%	95%	3%	13%	67%	10%	10% / 0%
4	0%	92%	8%	25%	75%	0%	0% / 0%
6	0%	81%	19%	5%	93%	2%	0% / 0%

Using the FLC with a PF4 appears to be very safe, reliable and avoids hypoglycemia. We plan a January 2011 IDE submission with expected patient studies with human adult patients in early 2011.

Supported by: JDRF

Clinical Diabetes/ Therapeutics PUBLISHED ONLY

2221-PO

Quality of Life and Subcutaneous Ambulatory Insulin Pump in Type 2 Diabetes Patients

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Does an insulin pump therapy in diabetic patients provide, beside a better metabolic control, an increase in quality of life, while remaining easy to use?

172 Type 2 diabetes patients (age: 58 ± 9.9 year, sex ratio M/F: 0.4, diagnosed for diabetes for 17.3 ± 9.0 years, weight: 94.4 ± 18.3 kg) switched to an ambulatory subcutaneous insulin pump therapy (glucose control failure in despite of 3 ± 0.7 insulin injections/day) are analyzed in an observational study.

172 patients went on with their insulin pump; 8.3% gave up with the pump and among the 96 patients followed after 1 year (T_1Y), 51 (53%) have agreed to answer and filled in a Quality of Life questionnaire.

The pumps that were used are of the following types: Accu check spirit (14.5%), Animas (12.5%), Cozmo (25%) and Medtronic (48%), and the most used Catheter was (n: 20-42.5%) the QUICK SET type.

The analysis on the patient's feeling towards the pomp can be classified in: poor – medium – good and concerns:

Table 1. Health status

	Good	Medium	Poor
Estimate of general state	40%	38%	22%
Limitation in physical activity and everyday life	32%	45%	23%
Moral state	30%	54%	16%

Table 2. Health status and pump (after 1year)

Pump therapy after 1 year, the analysis of the feeling towards the pump : learning and usage ease	Easy	~ Easy	Difficult
	51%	45%	4%
Evolutive feeling of the health status	74%	22%	4%
Efficacy provided by the pump on glycaemic status	**Yes**	**Better**	**Bad**
	47%	53%	-
Feeling and usage towards the pump	**Very good**	**~ Good**	**Bad**

Conclusion: The metabolic optimisation through insulin s /c pump after poor glucose corol in despite multi insulin injections treatment, lead, in a large majority of type 2 diabetes patients, to a great improvement of quality of life, with better physical and moral health. Almost all considers the use of the pump is simple. They are satisfied to a better experience and better control thanks to the latter.

2222-PO

Self-Assessment and Determination of Dexterity and Cognitive Function in Patients with Type 1 and Type 2 Diabetes Mellitus

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Insulin treated patients perform complex treatment activities during daily routine, such as blood glucose measurements or insulin injections. The goal of this study was to compare the patient self-assessment of their dexterity skills with the results of validated dexterity and cognitive function tests (Jepsen-Taylor-Hand Function Test, (JHFT) and the number connection test). The JHFT consists of 7 subtests, of which at least 4 need to be passed to be considered 'not impaired'. Also, neuropathy was assessed by means of heat, cold, pain, and vibration perception threshold determination (Medoc TSA 2001). We enrolled 90 patients (36 females, 54 males) from 4 different groups (15 type 1 with clinically suspected dexterity impairment (A; age: 60±9 yrs.; HbA1c: 6.9±0.7 %; BMI: 26.8±4.1 kg/m²), 30 type 2 with clinically suspected dexterity impairment (B; age: 61±10 yrs.; HbA1c: 7.5±1.2 %; BMI: 36.3±7.4 kg/m²), 30 type 1 or type 2 with visual impairment (C; age: 64±6 yrs.; HbA1c: 7.3±1.0 %; BMI: 32.5±6.9 kg/m²), and 15 type 1 or type 2 without any other concomitant condition (control group: D; age: 64±5 yrs HbA1c: 7.0±1.0 %; BMI: 30.5±5.5 kg/m²)). There were no major pathological findings in the neuropathy and cognitive function tests. Patient self-assessment revealed that all, but 2 patients from group B, considered themselves to have no dexterity impairment. When performing the JHFT with the dominant hand (normal age-related reference score: 5.5 s), all but the control group showed significant dexterity impairment in the mean JHFT score (A: 6.8±3.2 s; B: 6.8±3.2 s; C: 6.5±3.8 s; D: 5.8±3.8 s, $p<0.05$ v. all other groups). All patients from A and B, 33 % from C, and 0 % from D had impaired dexterity according to the individual JHFT criteria. Impairment of dexterity (independent from neuropathy or cognitive function) was more frequent than what the patients actually expected. It may be worthwhile to consider these findings when developing new diagnostic or therapeutic devices for patients with diabetes mellitus, as it may affect their individual performance with (and their preference for) a particular device.

Supported by: Novo Nordisk

2223-PO

Significant Improvement in Treatment Satisfaction for Patients (pts) with Type 1 and Type 2 Diabetes Mellitus (T1&T2DM) after 6 Months Following the Initiation of Insulin Glargine (Lantus SoloSTAR®)

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Insulin treatment improves long-term glycemic control. Insulin delivery devices could affect treatment satisfaction. The aim of this study was to evaluate the change in treatment satisfaction in pts treated with Lantus SoloSTAR® pen.

This 6-month Canadian, observational, multicenter, prospective registry collected data in 220 T1&T2DM pts from 32 sites. Pts treated with any combination of unmixed basal insulin, oral anti-hyperglycemic drugs or short-acting insulins who had an A1c>7% or an A1c≤7% with severe or frequent symptomatic hypoglycemia were enrolled. Treatment satisfaction was measured using the standard Diabetes Treatment Satisfaction Questionnaire at baseline (DTSQs) and after 6 months (DTSQc). Pts acceptance of SoloSTAR pen was assessed using 8-item pen use questionnaire having scores from 1=excellent to 5= very poor.

56 T1DM and 164 T2DM pts were on average 39.7 (SD=12.4) and 59.3 (SD=11.0) years old and had BMIs of 26.9 (SD=4.7) and 33.4 (SD=8.0) kg/m2, respectively. 162 (74%) pts were on basal insulin and 151 (69%) pts were using a pen at baseline. Overall satisfaction at baseline was 25.4 (SD=6.8).

ALL pts completed the DTSQc at the end of study. There was greater treatment satisfaction with a mean DTSQc score of 12.0 (SD=5.4). 211 (95.9%) of the pts had better satisfaction scores compared to baseline. The change in perceived hyperglycemia and hypoglycemia scores were slightly improved, -0.1 (SD=1.8) and -0.5 (SD=1.7), respectively. The total mean ease of use score for SoloSTAR® pen was 11.3 (SD=4.4) indicating excellent satisfaction. Mean A1c improved significantly from baseline (diff:-0.7, 95% CI:-0.92, -.055).

This real-life study demonstrates that in both T1&T2DM pts changing previous treatment to insulin glargine provided significant treatment satisfaction that was due to ease of SoloSTAR® pen use and significant better metabolic control as demonstrated by the subgroup analyses.

Supported by: sanofi-aventis, Canada **ADA-Funded Research**

2224-PO

Treatment of Impaired Glucose Tolerance with Buccal Spray Insulin: A 6 Months Randomised Controlled Trial

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In patients with impaired glucose tolerance (IGT), upon implementation of life style changes and metformin, a third returns to normal glucose tolerance, a third continues with IGT and the rest goes on to develop clinical type 2 diabetes. An increased risk for cardiovascular disease occurs in the latter two groups even though there is no progression to diabetes. A previous proof of concept study demonstrated that treatment with 12 puffs of buccal

For author disclosure information, see page 785.

ADA-Funded Research

spray insulin was followed by a significant 29.6% decrease in mean plasma glucose at two-hours and a 26.8% decrease at three-hours.

We have designed a randomized controlled trial in patients with IGT comparing buccal spray insulin (Ora-lyn) (12 puffs per meal) plus physical exercise and diet (treatment group A, n=16, HbA1c at entry 6.06% ± 0.5) vs. physical exercise and diet only (control group B, n=16, HbA1c at entry 5.9% ± 0.3). HbA1c levels, metabolic parameters and insulin antibodies were measured at baseline and every 3 months up to 6 months. Primary endpoint is the reduction of HbA1c of 0.3% at 6 month treatment between the experimental and the control group. Secondary endpoints include the evaluation of antibodies against insulin (IA), changes in body weight and number of hypoglycaemic events.

Subjects treated with buccal spray insulin achieved a significant reduction of HbA1c compared to the control group (Δ HbA1c 0'- 6 month -0.34%±0,1 vs +0.07%± 0,1 p =0,03). There was no significant difference in body weight and no hypoglycaemic or other adverse events were observed during the study period in both groups. No generation of IA was observed in subjects with IGT treated with buccal spray insulin.

These preliminary results indicate that buccal spray insulin is an effective treatment compared to diet + physical exercise in patients with IGT in reducing HbA1c without adverse effects. A larger trial is required to demonstrate the long term effects of this therapy.

Supported by: Generex **ADA-Funded Research**

2225-PO

WITHDRAWN

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—PHARMACOLOGIC TREATMENT OF DIABETES OR ITS COMPLICATIONS

2226-PO

WITHDRAWN

2227-PO

A Prospective, Observational, Multicenter Registry To Evaluate the Initiation of Basal Insulin in Patients with Type 2 Diabetes in India: A Sub-Analysis of the FINE Asia Study

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FINE Asia is a prospective, observational registry undertaken to evaluate the initiation of basal insulin in patients with type 2 diabetes mellitus inadequately controlled by oral antihyperglycemic drugs. This subanalysis reports data for the population in India.

Visits were planned at baseline and 3 and 6 months. Efficacy outcomes were changes in A1C and fasting blood glucose (FBG) from baseline to 6 months, differences between treatments, reasons for not achieving targets, and insulin doses. Safety outcomes were adverse drug reactions and hypoglycemia.

From March 2006 to January 2008, 709 patients with type 2 diabetes were enrolled from 79 centers; 681 patients were included (59.6% males; mean age, 54.9 ± 10.0 years; mean BMI, 27.4 ± 4.8 kg/m^2; mean diabetes duration, 9.8 ± 6.4 years; mean A1C, 9.4 ± 1.2%). Glargine and NPH were used as basal insulin by 94.3% and 5.0% of patients. At 6 months, significant reductions were seen for A1C (-2.3 %; $P < 0.0001$) and FBG (-94 mg/dl, $P < 0.0001$) in the overall population. Changes in mean A1C were similar across treatment groups; however, significantly more patients (44.2%) receiving glargine achieved A1C < 7% compared with NPH (23.5%) ($P = 0.0175$). At 6 months, mean daily doses were 16.3 ± 7.1 and 12.6 ± 3.7 for glargine and NPH, respectively. Increases in mean daily dose were glargine, 1.5 U and NPH, 5.6 U. Rates of hypoglycemic episodes over 6 months were lower with glargine (43 [6.7%]) than with NPH (5 [14.7%]), but the difference was not significant ($P = 0.1768$). Over 6 months, there were 4 episodes of severe hypoglycemia in the glargine group and 1 episode in the NPH group.

Insulin glargine resulted in A1C < 7% in a significantly greater percentage of patients than did NPH. Still, more than half of patients receiving glargine did not reach glycemic targets. Mean daily doses for glargine and NPH were substantially lower than in randomized clinical trials, suggesting potential for greater control and the need for improved compliance with international guidelines on the part of physicians and patients in India.

Supported by: sanofi-aventis

2228-PO

A Pulse of Insulin as the Initial Treatment of Type 2 Diabetes: Durability and Metabolic Effects

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Type 2 diabetes is a progressive disease. Despite the availability of many classes of medications glucose control is achieved in only about half of patients. To date, no treatment has proven to halt the disease progression as measured by beta cell function. Insulin as the initial treatment of type 2 diabetes is often used for patients with severe hyperglycemia but this approach is not applied as commonly in people with moderate hyperglycemia. Early studies have shown promise for controlling hyperglycemia and producing a "legacy effect". This case series demonstrates the authors experience with basal-bolus analog insulin as the initial treatment of type 2 diabetes. All patients were newly diagnosed and on no baseline oral therapy. Ten patients were treated with the insulin first protocol. Treatment consisted of basal bolus insulin replacement. Typically basal insulin was started at 0.3 units/kg/day. The equivalent dose of a rapid acting analogue insulin was divided into thirds to cover meal meals. Patients were instructed to send in readings weekly for titration. Basal insulin was titrated twice weekly and meal time insulin once weekly. This report describes 10 patients including nine men and one woman. The mean age was 54.4 years with a mean BMI of 30.5. The baseline HgA1C mean at diagnosis was 11.2% and was reduced to 6.4% post insulin to 6.1% at one year. Other improvements included weight neutrality at one year and improvement in lipids and increasing c-peptide over time. Three patients have now gone greater than 2 years without any pharmacologic treatment yet have maintained good glucose control with a HgA1c below 6.2%. This case series needs to be confirmed in a controlled trial. The INSPIRE DM trial sponsored by Sanofi-Aventis will address the efficacy of such a treatment.

2229-PO

WITHDRAWN

2230-PO

A Real-Life, Short-Term Efficacy of DPP-4 Inhibitor Sitagliptin in Japanese Patients with Type 2 Diabetes

NAKAYUKI YOSHIMURA, NOBUYUKI OGATA, TOMOMI MAEDA, YAMATO MASHIMO, MAIKO NUMAKURA, YUKO FUJIMAKI, YOKO OKA, TAKAOKI SUDA, TOSHIO ISHIKAWA, HIROKO OKINAGA, SHIN FUJIMORI, TAMIO TERAMOTO, KAZUHIRO ETO, *Itabashi, Japan*

A short-term efficacy of anti-diabetic DPP-4 inhibitor sitagliptin (SIT) was examined in Japanese patients with type 2 diabetes. SIT (45±20 mg) was administered to 114 patients (baseline: age; 62±12 years, M/F; 77/37, BMI; 25.9±4.5kg/m^2, duration of diabetes; 10.8±7.7 years, HbA1c; 8.19±0.95%) for 213±75 days. HbA1c descended to 7.11~7.19% between 150-240 days. At the last visit HbA1c was 7.32±0.93%, and HbA1c≤6.5% and ≤7.0% were accomplished in 18% and 46% of patients. Changes in HbA1c were -0.97±0.92%, -0.82±0.93% or -0.22±0.70% in patients treated with 25, 50 or 100 mg of SIT, respectively.

Weaker effects of SIT at 100 mg were attributed to additive dosages to lower responders. Patients treated with sulfonylureas (SUs) had higher baseline HbA1c (8.40±0.91 vs 7.68±0.86%) and longer duration of diabetes (13±8 vs 7±5 years) than without SUs, but both groups showed similar HbA1c changes (-0.87±0.90 vs -0.70±0.98%). Through this study, dosages of SUs were reduced or discontinued in 44% of patients and unchanged in 44% patients. There were no differences in HbA1c changes with or without use of pioglitazone, metformin or α-glucosidase inhibitors. When HbA1c changes were stratified by quartile division, the best responder group (-1.99±0.63%),

For author disclosure information, see page 785.

as compared to the worst responder group (0.21±0.57%), had higher baseline HbA1c value (9.02% vs 7.72%). However, there were no differences in dosages of SUs, duration of diabetes or BMI between the groups.

Addition of SIT to patients who had already been receiving three OADs (more than half maximal dosage of SUs, metformin and pioglitazone) was effective in reducing HbA1c (n=17, baseline HbA1c; 8.61±0.86%, final HbA1c; 7.56±0.81%, changes; -1.05±1.08%, accomplishment of ≤7.0%; 29%). As a whole, body weights (0.2±2.7 kg) or blood pressure (sBP; -0.5±16 mmHg, dBP; 0.4±10 mmHg) did not change significantly during the study. Changes of body weights were not correlated with those of HbA1c. In Japan a real-life efficacy of DPP-4 inhibitors has not been fully elucidated since their introduction to clinical practice at the end of 2009. This study clarified basic characteristics of SIT, which would expand options for treating type 2 diabetes in Japanese.

2231-PO

WITHDRAWN

2232-PO

Acarbose Attenuates Postprandial Hypotension in Older Adults with Type 2 Diabetes Mellitus

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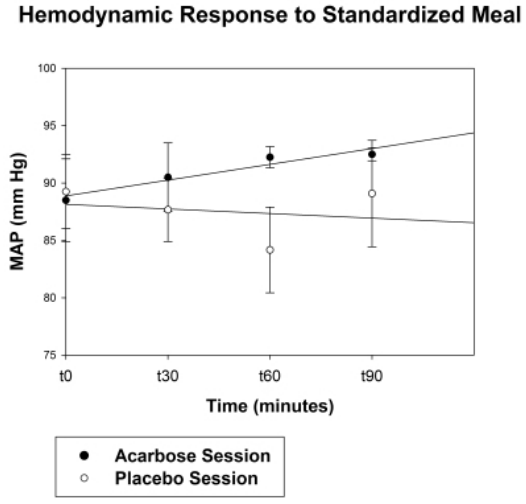
Postprandial hypotension (PPH) has been documented to occur in up to 40% of people with Type 2 Diabetes Mellitus (T2DM) and can precipitate falls due to syncope. To date there are no reliable treatments for this condition. It was our objective in our pilot study to demonstrate that acarbose, an alpha-glucosidase inhibitor, decreases the degree of PPH in the elderly diabetic population.

5 adults (age≥65 years) with T2DM were recruited and attended both a treatment and placebo session in random double-blinded order. Subjects were fed a standardized meal and were then monitored over 90 min with continuous monitoring of blood pressure by Finometer and continuous heart rate monitoring by three lead electrocardiogram. Subjects receiving placebo demonstrated a decrease in mean arterial pressure (MAP) of 10±2 mm Hg after 60 minutes as compared to an increase in MAP of 8±2 mm Hg in the acarbose group. The hemodynamic response of MAP to the standardized meal was significantly different between the placebo and acarbose sessions by two-factor repeated measures analysis of variance (p=0.047, Figure 1).

Our study demonstrates that acarbose attenuates PPH in persons with T2DM, resulting in less hypotension after administration of a standardized meal. Although preliminary, this suggests a future treatment to prevent PPH in this vulnerable population.



Supported by: Canadian Institutes of Health Research

2233-PO

Achieving Reductions in HbA1c ≥1% without Hypoglycemia with Saxagliptin Combination Therapy: Post Hoc Analysis of 4 Randomized Controlled Studies in Patients with Type 2 Diabetes

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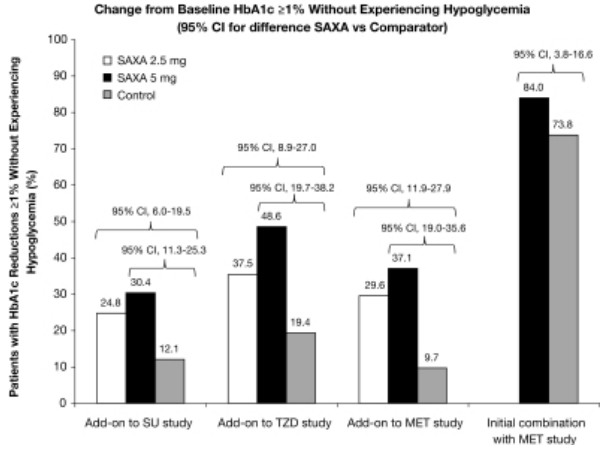
Currently available dipeptidyl peptidase-4 (DPP-4) inhibitors typically provide mean reductions in glycated hemoglobin (HbA1c) of 0.6%–0.8%. Based on the glucose dependency of their mechanism of action, limited risk for hypoglycemia has been observed in clinical trials. In 4 pivotal randomized, double-blind clinical trials, the primary efficacy and safety of the DPP-4 inhibitor saxagliptin (SAXA) as an add-on to the sulfonylurea (SU) glyburide, a thiazolidinedione (TZD), or metformin (MET) vs placebo (PBO) and as initial combination of SAXA+MET vs monotherapy with MET have been reported. In these trials, baseline demographic and glycemic parameters were balanced between treatment groups. A post hoc analysis of these 4 studies (n=3382) was undertaken to further characterize the benefit/risk of SAXA and specifically addressed the proportion of patients achieving higher than average HbA1c reductions (last observation carried forward) defined as ≥1% as add-on and initial combination therapy with MET and ≥2% as initial therapy with MET without reported hypoglycemia at 24 weeks. The SAXA arms were compared to the control using exact CIs. The percentage of patients achieving HbA1c reductions ≥1% without hypoglycemia are shown in the Figure.



In addition, 65.7% of treatment-naïve patients achieved HbA1c reductions ≥2% without experiencing hypoglycemia with SAXA 5 mg + MET vs 47.3%

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ADA-Funded Research

treated with MET alone (95% CI for difference vs MET + PBO, 10.6%–26.0%). In summary, a greater proportion of patients receiving SAXA as add-on therapy with other oral antidiabetic drugs or as initial combination therapy with MET achieved reductions in HbA1c of ≥1% and ≥2%, respectively, without experiencing hypoglycemia.

2234-PO

Additional Glucose-Lowering Effects of the Oral GK Activator, MK-0941, in Patients with T2DM on Basal Insulin

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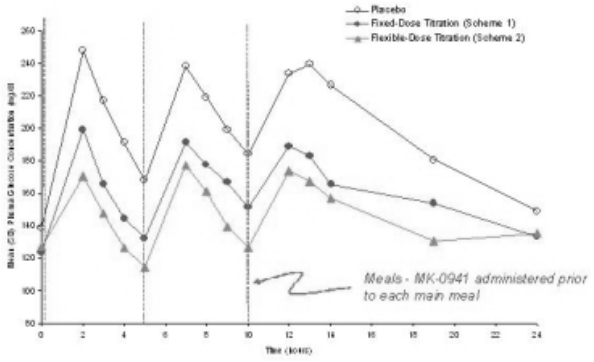
MK-0941 is an orally active, selective, potent allosteric GK activator. In a randomized, double-blind, placebo-controlled study, the safety, pharmacokinetics and pharmacodynamics of MK-0941 administered 3 daily prior to each main meal was assessed in patients with T2DM on basal insulin. At screening patients (n=70) had HbA_{1c} ≥7.0% and ≤11.0% and were on intermediate- or long-acting insulin, which was converted to similar doses of insulin glargine (Lantus) and maintained with a target FPG between 130 and 280 mg/dL, prior to randomization. Patients received MK-0941/PBO in a 2:1 ratio and were assigned to either "fixed titration" (same pre-meal doses, with dosing initiated at 10 mg on Day 1) or "flexible titration" (potentially different pre-meal doses, with dosing initiated based on a "sliding scale"). Pre-meal doses of MK-0941 were increased by 5- to 10-mg daily on Days 2 - 4, based on pre-meal glycemic criteria, to a maximum of 40 mg/dose. Patients received individualized Day 4 doses for another week prior to glycemic assessment when MK-0941 was associated with an ~ 48 mg/dL ($p<0.001$) reduction in 24-hour weighted mean glucose (WMG). Dosing was continued to evaluate longer-term safety and tolerability. MK-0941 was well tolerated for up to 25 days of administration: no consistent, clinically relevant, treatment-related effects on ECGs, vital signs or laboratory safety tests were observed. Hypoglycemia occurred primarily prior to lunch and was clinically manageable, short in duration with subsequent episodes mitigated by dose reductions. In conclusion, in this ~4 week study, MK-0941 was associated with a statistically significant additional reduction in 24-hour WMG concentrations in patients with T2DM on insulin glargine. While these results appear promising, studies up to 30 weeks demonstrated time-dependent loss of MK-0941 efficacy.



2235-PO

Alogliptin Decreases Liver Fat Content in Patients with IGT or Type 2 DM: Comparing Alogliptin and Voglibose

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Nonalcoholic fatty liver disease (NAFLD) is frequently associated in patients with type 2 DM. We recently reported that Nateglinide (NAT) or Pioglitazone(PIO) treatment ameliorates both postprandial hyperglycemia and NAFLD, but Voglibose (VOG) does not. To clarify whether Alogliptin(ALO), new anti-diabetic drug may decrease liver fat content, the 35 patients with NAFLD comprised of 24 IGT and 11 DM were recruited. The 35 patients were randomly assigned to the treatment for 12 wk with Alo (25mg daily) or VOG (0.6mg daily). A 75-g OGTT, laboratory measurements and computed tomography (CT) to determine liver CT values (Hounsfield unit, HU) were performed at baseline and after the treatment. Early insulin secretion and postprandial hyperglycemia were assessed by delta IRI / delta PG for 30 min and the area under a curve (AUC) of glucose excursion for 120 min after a glucose load. Liver CT values and spleen CT values were evaluated in terms of the mean values for three different sites respectively. After the treatment, the AUC of glucose was significantly decreased in both groups as compared with those of the baseline. However ALO administration showed higher liver CT values (ALO: 48.8±10.2,54.3±8.9HU P<0.01), the liver-to-spleen ratio (ALO: 0.87±0.16,0.98±0.15 P<0.01), as compared with those of the baseline but VOG does not. ALO treatment also showed higher IRI/PG(0.68±0.37, 1.34±1.37 P<0.05), HDL-c (49.4±14.8, 52.2±13.3 mg/dl P<0.05) and lower TG (143.0±53.9, 115.2±41.3 mg/dl P<0.01), ALT(23.2±3.8,18.8±6.5 U/l P<0.01) as compared with those of the baseline. In ALO group, before and after treatment, there were also no differences in BMI, HOMA-IR. In conclusion, Alogliptin may decrease liver fat content and may be beneficial for the treatment for NAFLD in patients with IGT or type 2 DM.

2236-PO

Analysis of Insulin Doses of Chinese Type 2 Diabetic Patients on Intensive Insulin Treatment

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Objective: To investigate the daily insulin doses and the ratio of basal/total daily insulin in Chinese type 2 diabetic patients who received basal bolus insulin therapy. Methods: 1683 hospitalized patients receiving pre-meal bolus insulin (Humulin R) and bedtime basal insulin (Humulin N) were included. Results: The mean fasting glucose level of incharge was 8.61±2.95 mmol/L and 7.31±1.86 mmol/L when discharge from hospital, and mean 2h postprandial glucose level of incharge was 13.58±4.98 mmol/L and 8.63±2.47 mmol/L when discharge from hospital.

variables	insulin dose	basal insulin doses	bolus insulin doses	BD/TDD ratio
	r(P)	r(P)	r(P)	r(P)
age	-0.102(0.018)	-0.366(0.003)	-0.056(0.201)	-0.146(0.001)
DM duration	0.207(0.000)	0.309(0.011)	0.172(0.000)	0.115(0.011)
HbA1c	0.204(0.000)	0.220(0.051)	0.183(0.000)	0.052(0.226)
Fasting C peptide	-0.032(0.439)	0.009(0.938)	0.009(0.826)	-0.171(0.000)
Postprandial C peptide	-0.009(0.792)	0.020(0.818)	0.027(0.416)	-0.154(0.000)
FBG(Incharge)	0.014(0.733)	0.081(0.512)	-0.012(0.761)	0.114(0.006)
PBG(Incharge)	0.014(0.735)	0.137(0.248)	0.016(0.688)	-0.021(0.608)

The mean daily insulin doses was 37.28 IU/day, the mean daily insulin doses per weight was 0.59 IU/kg, mean basal/total daily insulin ratio (BD/TDD) was 0.22. In most patients (47.65%), the BD/TDD was 0.20 to 0.30. Of the patients receiving insulin therapy alone or receiving insulin combination with metformin, the BD/TDD ratio between 0.20 and 0.30 were very similar (45.94% and 49.25% respectively). With the increasing of the BD/TDD ratio, the total insulin doses increased, the insulin doses per weight increased, the age of patients decreased, and fast and postprandial C-peptide decreased. Conclusions: The daily insulin doses of intensive treatment in Chinese type 2 diabetic patients was 37.28 IU/day, the mean daily insulin doses per weight was 0.59 IU/kg, mean BD/TDD ratio was 0.22.

2237-PO

Assessment of Reproducibility of the Diabetes Intervention and Management with Excellence (DIME Program©) Care Model: A 1-Year, Prospective Evaluation of Performance Improvement Utilizing EHR-Data Analysis along with a Diabetes Chronic Care Model

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The results of the DIME Program© Care Model (DPCM) were previously published and demonstrated the proof of concept that its application can improve the achievement of measured ADA goals. A test clinic (11 PCPs) was selected to validate these results. A 12 mos retrospective analysis for baseline EHR performance was reported. The DPCM was implemented followed by 4 quarterly reports to evaluate performance improvement on HbA1C, blood pressure (BP) and LDL cholesterol (LDL) while applying suggested treatment algorithms and performance improvement Tools (The DIME diabetes protocol, Quarterly patient registries, eA1C conversion table, BP/LDL algorithms, insulin titration tables, and insulin pump initiation/management protocols). We report data for baseline and quarterly findings for HbA1C, BP, LDL and insulin pump use. All pts had an ICD-9 code 250. Results are shown in Table 1.

Compared to baseline, all but 1 variable (LDL ≥130) were improved at Q4. All ADA measured goals were acheived by Q4. 5 PCPs initiated 19 pumps.

Table 1. % of pts who achieved selected ADA goals and pump use.

Variable	Baseline n= 1,008	Q1	Q2	Q3	Q4* n=1,290
%HbA1C	%	%	%	%	%
<7	51	48	45	69	71
>9	6	6	4	5	5
BP (mmHg) <130/80	37	58	45	45	43
≥140/90	28	24	22	27	26
LDL (mg/dl) <100	32	30	33	59	38
≥130	7	7	15	13	12
No. of Insulin Pumps	0	0	4	9	19
No. of managing PCP's	0	0	3	5	5

*n increased as pts added to DPCM.

These data validate the results that achievement of measured ADA goals can be improved with the DPCM/EHR-data reporting. 45% of the PCP's initiated insulin pump therapy. The significance of this finding and insulin pump protocols with PCPs requires further study.

Supported by: Eli Lilly

2238-PO

Baseline Characteristics from 11 Prospective Randomized Trials That Predict an Effective Approach To Starting and Adjusting Insulin Glargine

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Insulin glargine (GLAR) can be added to patients with type 2 diabetes (T2DM) inadequately controlled by oral agents, yet the most effective and safe starting dose or the maximum dose to reach endpoint glucose targets in a given patient is unclear. This analysis examined whether baseline characteristics can predict appropriate GLAR starting and final dosages in T2DM patients. Data were pooled from 11 prospective, 24-week, randomized, controlled trials (N=2311) using basal GLAR as the only insulin. Strict, predefined insulin titration algorithms were followed to achieve FPG ≤100 mg/dL. Mean age was 58.6 years, 55.8% were male, and 81.6% were white. The Table shows Week 24 weight-adjusted insulin doses, % of patients achieving A1C ≤7%, and yearly rates of severe hypoglycemia. GLAR requirements increased in obese (BMI >30) vs non-obese patients and in patients with greater baseline A1C. GLAR requirements decreased in elderly (≥65 yrs) vs non-elderly (<65 yrs) patients. Week 24 target A1C (≤7%) was reached by ~65% with baseline A1C <9%; ~40% with A1C ≥9%. Yearly event rates of severe hypoglycemia were generally low in all groups; rates were slightly higher with higher baseline A1C. In the elderly, a 0.1 U/kg starting dose can be safely titrated to 0.3-0.4 U/kg to reach target endpoints. In the nonelderly, if A1C is <9% start with 0.1 U/kg and adjust to 0.4 U/kg; if A1C is ≥9% start with 0.2 U/kg and adjust to 0.5-0.6 U/kg. While GLAR dosages should be determined by the physician based on individual patient characteristics, these baseline predictor data from a large patient pool provide clinically relevant guidelines for starting and adjusting GLAR dosages that allow patients to reach glycemic targets safely (minimizing severe hypoglycemia).

	<65 years		≥65 years	
Baseline A1C	**Non-obese**	**Obese**	**Non-obese**	**Obese**
Week 24 weight-adjusted insulin dose (U/kg) (Mean [SD])				
<9%	0.38 (0.22)	0.45 (0.25)	0.33 (0.19)	0.34 (0.17)
≥9%	0.49 (0.25)	0.58 (0.29)	0.41 (0.21)	0.39 (0.20)
Week 24 A1C ≤7% (n/N, %)				
<9%	260/388 (67.0)	357/516 (69.2)	149/235 (63.4)	106/158 (67.1)
≥9%	109/286 (38.1)	146/365 (40.0)	53/129 (41.1)	36/93 (38.7)
Severe hypoglycemia (events/year) (Mean [SD])				
<9%	0.02 (0.18)	0.08 (0.62)	0.07 (0.80)	0.03 (0.25)
≥9%	0.15 (1.87)	0.01 (0.16)	0.00 (0.00)	0.02 (0.23)

Supported by: sanofi-aventis US

2239-PO

Baseline Risk Factors for Weight Gain in People with Type 2 Diabetes Mellitus Beginning Insulin Therapy in the CREDIT Study

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Insulin use is often associated with weight gain. We evaluated risk factors for weight gain in the CREDIT study, a 314-center, multinational, noninterventional study of people beginning insulin therapy that enrolled 3031 people with type 2 diabetes mellitus, 52% beginning with basal insulin alone, 23% on pre-mix insulin, and 25% on other insulins. Median weight gain after 1 year was 1.6 kg (n = 2442). Potential baseline measures associated with weight gain ≥ 1.6 kg were described and assessed by stepwise logistic regression. To enter and retain each factor in the model required a *P* value of ≤ 0.20 and ≤ 0.05, respectively. In the final multivariable model (n = 2312), baseline A1C had a positive effect, as did lower BMI (Table). Female gender, presence of micro- or macrovascular disease, and taking ≥ 3 (vs 0) glucose-lowering medications at baseline predicted weight gain. Baseline physical inactivity and a diagnosis of high blood pressure were inversely related to weight gain. We conclude that in real-life clinical practice factors others than those traditionally associated with weight gain on starting insulin are important and could be used to target those at particular risk.

Variable	**Odds Ratio***	**95% CI**	***P***
Gender (female vs male)	1.51	1.24-1.83	< 0.001
BMI (kg/m^2)	0.92	0.91-0.93	< 0.001
≥ 1 microvascular disease (yes vs no)	1.27	1.01-1.60	0.042
≥ 1 macrovascular disease (yes vs no)	1.26	1.04-1.53	0.017
Diagnosed high blood pressure (yes vs no)	0.75	0.61-0.92	0.007
Physical activity (no vs yes)	0.77	0.64-0.92	0.005
A1C (%)	1.14	1.08-1.20	< 0.001
Glucose-lowering medications (≥ 3 vs 0)	1.91	1.27-2.85	0.002

*Country adjusted

Supported by: sanofi-aventis

2240-PO

BCG Treatment of Long-Term Type 1 Diabetics

DENISE L. FAUSTMAN, LIMEI WANG, YOSHIAKI OKUBO, DOUGLAS E. BURGER, LIQIN BAN, GUOTONG MAN, HUI ZHENG, DAVID SCHOENFELD, RICHARD POMPEI, JOSEPH AVRUCH, DAVID M. NATHAN, *Charlestown, MA, Boston, MA*

No targeted immunotherapies exist for reversing advanced type 1 diabetes. *Bacillus-Calmette-Guerin* (BCG), which induces release of tumor necrosis factor (TNF), has been used successfully in rodent models to reverse disease by specifically removing autoreactive T cells and unleashing pancreas regeneration to restore long-term normoglycemia. In murine models of type 1 diabetes, this therapeutic intervention is unique in removing beta-cell autoimmunity and improving glycemia even in animals with near complete eradication of beta-cell function, and not just in new onset diabetes.

In this proof-of-principle, phase I trial, we treated adult patients with long-term type 1 diabetics with BCG, a non-virulent genetic vaccine, to determine whether BCG depletes the disease-causing autoimmune cells and identify any pancreatic beta-cell responses. We randomly assigned patients with long-term type 1 diabetes (mean 15-years duration) to repeated BCG vaccinations (n=3) or placebo (n=3) in this 20-week double-blinded placebo-controlled trial and compared them to subjects without diabetes (n=6). We measured blood samples for autoreactive T cells, T_{REG} cells, GAD autoantibodies, and C-peptide, a marker of insulin secretion. Another group of patients with type 1 diabetes (n=58) and nondiabetic (n=17) subjects served as reference subjects for the T cell and other assays. BCG-treated patients and one placebo-treated patient who unexpectedly developed an acute Epstein-Barr virus infection, another known inducer of TNF, exclusively showed transient increases in the number of circulating dead autoreactive T cells against insulin. In two of the BCG subjects and the EBV-infected subject, C-peptide levels rose transiently above baseline levels to a statistically significant extent in comparison to longitudinally followed C-peptide in reference subjects.

BCG-treatment or EBV-infection transiently modified the autoimmunity that underlies even advanced type 1 diabetes, suggesting that similar therapy may have value in the treatment and even reversal of advanced type 1 diabetes. Larger trials are necessary to extend these results and identify the most effective doses and frequency of BCG treatment.

For author disclosure information, see page 785.

2241-PO

Between Dose Settings with Liraglutide (Victoza) Pens: Are 5 "Clicks" Equal to Midway Dose?

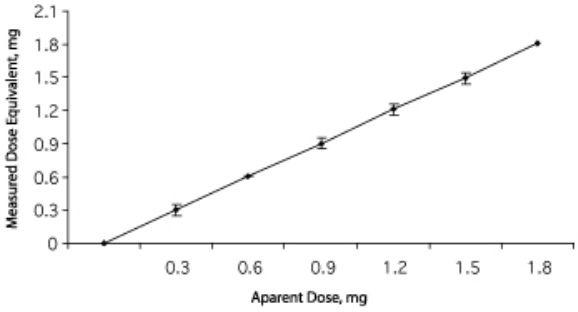
THERESA LINEHAN, GARY WOLFE, ALLEN KING, *Salinas, CA*

The liraglutide dosing pens are demarcated into dosing amounts of 0.6, 1.2 and 1.8 mg. Occasionally the side effects of a higher dose and the ineffectiveness of a lower dose suggest an intermediate dose or between dose setting. Since there are 10 'clicks' between dose amounts, 5 'clicks' would be half way and presumably result in the desired mid-dose. But do they?

We evaluated the volume from 6 liraglutide pens in a randomized order at six apparent doses: the demarcated doses of 0.6, 1.2 and 1.8 and at the apparent between doses as measured as 5 'clicks' of 0.3, 0.9 and 1.2 mg. The dose was delivered from the pen using a 32 g needle into a Mohr 1 ml graduated pipette (accuracy ± 0.01 ml). The volume measurement was converted to mg by the stated concentration of liraglutide, 6 mg/ml.

The mean and 95% CI are displayed in the graph below.

Using 5 pen 'clicks' accurately delivered a dose that is half way between the indicated mg doses. This conclusion is tempered by the small size of this study, the possible inaccuracy of the assessment method and the off-label dosing of this product.



2242-PO

WITHDRAWN

2243-PO

Brain Signaling of Long-Acting Insulin Analogues Glargine and Detemir for the Regulation of Glucose Metabolism and Learning/Memory in Mice

HIROSHI TSUNEKI, NORIHIKO MORI, SHUJI HOSOH, TSUTOMU WADA, TOSHIYASU SASAOKA, *Toyama, Japan*

Central insulin action plays a crucial role in the regulation of whole-body glucose homeostasis and learning/memory function. However, the effect of long-acting human insulin analogues glargine (Gla) and detemir (Det) in the central nervous system is largely unknown. The aim of the present study was to investigate the signaling properties of Gla and Det in the mice hypothalamus, hippocampus and cerebral cortex, relevant to the homeostatic and memory functions in brain. Intracerebroventricular (i.c.v.) injection of Gla, Det, and human insulin (10 mU/mouse) induced similar increase in phosphorylation of hypothalamic Akt and hepatic STAT3 in mice, implicated in whole-body glucose homeostasis. Blood glucose levels were unaffected by these treatments. In contrast, insulin and Gla were more potent than Det in increasing the phosphorylation of Akt in the hippocampus and cerebral cortex 3 h after the i.c.v. injection (the rank order of potency was insulin=Gla>Det). Interestingly, however, i.c.v.-injected Det induced a rapid increase in the phosphorylation of CREB, an important transcription factor implicated in memory formation, compared to Gla and insulin through unknown mechanism. In addition, Det augmented memory function in mice more evidently than Gla and insulin at 30 mU in a step-through passive avoidance test. In diabetic db/db mice, i.c.v. injection of these insulins increased the levels of Akt phosphorylation in the hypothalamus, hippocampus and cerebral cortex, comparable to those in control mice. However, Det failed to increase the CREB phosphorylation in the hippocampus of db/db mice, whereas insulin slightly and Gla significantly increased it. These results suggest that although Gla and Det have a similar impact on the hypothalamic-liver network for the regulation of glucose metabolism, Gla is an insulin analogue physiologically more similar to human insulin than Det with regard to the signaling property in higher brain regions and memory performance in mice.

Supported by: sanofi-aventis

2244-PO

Changes in Glycemic Control over 26 Weeks with Basal-Supported Oral Treatment (BOT): An Observational Study in Hungary

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This 26-week open-label, observational, multi-centre cohort study was undertaken in Hungary to evaluate the efficacy and safety of insulin glargine in patients inadequately controlled on oral antihyperglycemic drugs (OADs) following the treatment paradigm Basal-supported Oral Treatment (BOT).

Demographic and anthropometric data, prior antidiabetic treatment, blood glucose and A1C values, hypoglycemic episodes and insulin dose were recorded. In addition, treatment satisfaction was assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

A total of 2507 patients from 148 outpatient clinics participated in the study from 2008 to 2009. Patients were equally divided among male and female and had mean age 59.7 ± 10.6 y, mean body mass index (BMI) 30.49 ± 4.47 kg/m^2. Before study entry 35% of the patients were on metformin monotherapy, 36% were on sulfonylurea monotherapy, 20% were on metformin-sulfonylurea combination therapy, and 9% were on other mono or combination therapies. At baseline, mean A1C was 9.0 ± 1.3%, and fasting blood glucose (FBG) was 10.5 ± 2.6 mmol/L. Mean glargine dose at initiation was 12.6 ± 6.0 IU. At 26 weeks, mean A1C decreased to 7.3 ± 0.8%, and mean FBG decreased to 6.9 ± 1.4 mmol/L, while glargine dose increased to 19.5 ± 8.2 IU. In addition, mean post-prandial glucose decreased from 11.4 ± 2.4 mmol/L at baseline to 8.1 ± 1.4 mmol/L at 26 weeks. At 26 weeks, 42.5% of patients had reached A1C ≤ 7%. Mean BMI decreased slightly to 30.3 ± 4.4 kg/m^2. Overall, 18 severe but non-life-threatening hypoglycemic episodes were reported by 15 patients during the study period. DTSQ scores showed improvement in all domains over the time of treatment with glargine.

These data highlight that sulfonylureas are still significantly present in the treatment of patients with type 2 diabetes in Hungary. This non-interventional study demonstrated the efficacy and safety of once daily insulin glargine supplemental to OADs without weight gain and with low incidence of severe hypoglycemia, following a BOT paradigm in a large set of patients.

Supported by: sanofi-aventis

2245-PO

Characteristics Associated with Glycemic Response to Insulin Therapy Initiation for Type 2 Diabetes

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Although any glycemic target is possible with insulin therapy, a minority of patients achieve A1C < 7% when initiating insulin. We studied glycemic response to newly initiated insulin therapy in a contemporary sample of type 2 diabetes patients.

We selected 1126 members of Kaiser Permanente Northwest who initiated insulin therapy January 2009-June 2010 for treatment of type 2 diabetes, requiring at least one year of health plan eligibility to ensure the 1st insulin dispense represented new therapy. The outcome of interest was achievement of A1C < 7% within 6 months of insulin initiation. We explored demographic and clinical characteristics that might correlate with glycemic response to insulin including age, diabetes duration, BMI, pre-insulin A1C, insulin dose (units per day), type of insulin used (fast-acting, regular, NPH, mixed, or long-acting), and prior and concomitant oral agents. We used multivariable logistic regression to isolate the independent contribution of these variables to the probability of achieving A1C < 7%.

Mean age of patients was 64+/-10 years and 53% were women. Of the 1126 patients, 400 (35.5%) achieved A1C < 7% following insulin initiation. Older age (66.7 vs. 62.5 years, p<0.001), shorter diabetes duration (8.3 vs. 9.2 years, p<0.001), and lower A1C prior to insulin (7.9% vs. 9.4%, p<0.001) were associated with achievement of <7%. Patients who achieved <7% did so with fewer units per day (45.3 vs. 54.4 u/day, p<0.001), less use of long-acting insulin (28.4% vs. 35.9%, p=0.006) and less concomitant metformin (43.8% vs. 50.5%, p=0.027). In multivariable analysis, each 1% of A1C prior to insulin was associated with a 34% reduction in the probability of achieving A1C <7% after controlling for insulin dose and type of insulin used

For author disclosure information, see page 785.

(OR 0.66, 95% CI 0.60-0.73). Age, sex, BMI and presence of comorbidities including cardiovascular disease, stroke, chronic kidney disease and heart failure were not statistically significant predictors of goal achievement.

In this observational study of real-world clinical practice, initiation of insulin therapy while A1C was still relatively low was the strongest predictor of achieving the glycemic goal of A1C <7%.

2246-PO

Characteristics of 833 Patients Newly Treated with GLP-1 Analogs or DPP-IV Inhibitors in 38 Diabetes Specialized Medical Practices in Germany

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Patients participating in Randomized Controlled Trials (RCTs) are a highly selected group of patients in contrast to those treated in daily life in Diabetes Specialized Medical Practices (DSP). We set-up a register in Germany to evaluate in which patients with Type 2 diabetes diabetologists initiate a antidiabetic therapy with GLP-1 analogs (GLP-1) or DPP-IV inhibitors (DPP-IV) to study the benefits of this is in daily practice. In 38 participating DSPs such an incretin therapy was started in 833 patients (402 female, 48.3%) over a period of 6 month (between April 2010 and September 2010). The characteristics of these patients at baseline were: mean (±SD) age 57±11 years, duration of diabetes 8.4±6.4 years, HbA1C 8.2±2.1%, BMI 36.7±7.6 kg/m^2. Most patients (63%) were between 50-70 years of age; however, also 57 patients had an age <40 years. Duration of diabetes was <10 years in most patients (72%); however, 38 patients had a duration of >20 years.

Quality of metabolic control was good or moderate in most patients (<9% in 68%); however, 19% had a bad metabolic control with an HbA1C >10%. Most of the patients were obese (25% with a BMI between 35-40 kg/m^2), but a considerable number was grossly overweight (16% with 40-45 and 13% >45 kg/m^2).

84.3% of the patients were on metformin therapy, 38.9% on insulin therapy and 24.1% on SUH therapy when treatment with DPP-IV or GLP-1 was started. Major indication (multiple choice possible) for starting incretin based therapy was quality of metabolic control (71.8%), overweight (66.9%) or patients request (23%). The GLP-1 analog chosen most often was liraglutide (43% of all patients), followed by exenatide in 7%; the DPP-IV inhibitor most often chosen was sitagliptin (37%), followed by vildagliptin (9%) and saxagliptin (4%). These data show that many patients treated in daily practice with this class of antidiabetic drugs would not have been included in RCTs. Subsequent follow-up analysis will show which patients benefit from incretin based therapy or do not. This might also be of help to characterize the group of patients which takes most advantage by incretin therapy drugs.

2247-PO

Clinical Experience with Liraglutide: The First 100 Patients

GARY WOLFE, ALLEN KING, *Salinas, CA*

Liraglutide, a GLP-1 analog, increases glucose-dependent insulin release, decreases glucagon, reduces appetite, increases satiety and is associated with weight loss. We wish to report our Clinic's first experience with this medication.

The charts of the first 100 consecutive diabetic patients who were started on liraglutide were reviewed. Liraglutide was initiated as 0.6 mg/d and increased to 1.2 mg/d in one week. Patients were encouraged to reduce their intake of food and to increase activity. Last observation was carried forward.

The mean age was 55.1 ± 11.1 years and A1C, 7.54 ± 1.54 %. 56% were female. The concurrent diabetic medications (some in combination) were thiazolidinedione (38), sulfonylurea (55), metformin (82), and insulin (39). Of the 100 patients started on liraglutide; 19 did not return for follow up; 11 discontinued due to side effects (abdominal pain, 2; urticaria, 2; nausea/vomiting, 7); 6, to lack of effect; and 8, to lack of insurance coverage. Of the 56 patients completing 12 weeks of therapy, 35 were switched directly from exenatide. For those not switched from exenatide, the Hb A1c decreased from 7.68% to 6.84% and weight fell from 111.4 to 109.0 kg, p = 0.006 and p <0.001 respectively. In those switched from exenatide, the Hb A1c decreased from 7.44 to 7.00 % and the weight fell from 105.8 to 103.6 kg, both p <0.001. Side effects of those who remained on liraglutide were mild and decreased over time.

In the setting of clinical practice, liraglutide treatment results in a significant reduction in weight and Hb A1c even in those transferred from exenatide.

2248-PO

WITHDRAWN

2249-PO

WITHDRAWN

2250-PO

Comparative Efficacy and Safety of Long-Acting Insulin Analogs in Patients with Type 2 Diabetes Failing on Oral Therapy: Systemic Review and Meta-Analyses

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Although long-acting insulin analogs are recommended in patients with type 2 diabetes failing on oral agents, their efficacy is uncertain. We compared efficacy and safety of regimens based-on long-acting insulin analogs with other preparations in insulin-naïve patients with type 2 diabetes failing on oral agents. Data from 9,548 participants in 22 English studies were included. In terms of decreasing hemoglobin A1c, long-acting insulin analogs were not statistically significant to rapid-acting insulin analogs or neutral protamine Hagedorn (NPH) insulin or glucagon-like peptide-1 (GLP-1) analogs, and the differences between long-acting insulin analogs and biphasic insulin analogs were marginal (weighted mean difference: 0.19%).Compared with rapid-acting insulin analogs, long-acting insulin analogs were similar in the incidence of total hypoglycemia and the superiority in less weight gain was inconsistence. Relative to biphasic insulin analogs, long-acting insulin analogs were associated with lower incidence of total hypoglycemia and less weight gain. Compared with NPH insulin, long-acting insulin analogs were associated with lower incidence of total and nocturnal hypoglycemia. Subgroup analysis revealed that detemir, but not glargine, was associated with less weight gain over NPH insulin. Relative to GLP-1 analogs, long-acting insulin analogs were associated with lower incidence of treatment related adverse events but with greater weight gain. For patients with type 2 diabetes failing on oral agents, initiating long-acting insulin analogues seems to provide glycemic control similar to rapid-acting insulin analogs or NPH insulin or GLP-1 analogs and slightly inferior to biphasic insulin analogs with fewer side effects.).

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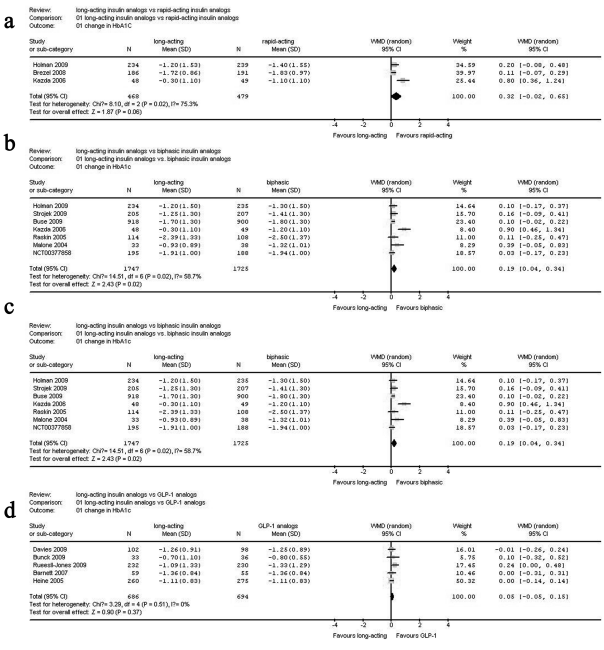

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2251-PO

Comparison of Efficacy and Safety in Patients Treated with Asparte Insulin or Lispro Insulin in External Pump

VANESSA LUBIN, FRANÇOISE PLAT, BLANDINE DELENNE, CATHY MATTEI, OLIVIA RONSIN, JACQUES COHEN, VÉRONIQUE DI COSTANZO, CATHERINE ATLAN, DENIS RACCAH, MARIE FRANÇOISE JANNOT-LAMOTTE, *Puyricard, France, Avignon, France, Aix En Provence, France, Marseille, France, Toulon, France*

The purpose of the study was to compare effectiveness and safety in 2 groups of patients treated with continuous subcutaneous insulin infusion (CSII), one with asparte insulin and the other with lispro insulin.

Among patients followed in "Diabète-Provence Network", a multicentric network of Department of Endocrinology in the south of France, data were obtained for 245 diabetic patients during their annual evaluation.

One hundred seventy three patients (82,1% type 1 diabetes, 15.5% type 2 diabetes and 2,4% other types of diabetes, aged 40.0±15.3 years, sex ratio 64M/109 W, diabetes duration 14.9±10.3 years) were treated with asparte insulin for 4.9±4.3 years, and 172 patients (78.8% type 1 diabetes, 17.6% type 2 diabetes, and 3,6% other types of diabetes, aged 42.2±14.6 years, sex ratio 65 M/107 W, diabetes duration 14,6 ± 8,7 years) with lispro insulin for 4.4±4.1 years. Pump indications for the two groups were respectively: HbA1C>8% (45.3% vs. 34.8%); glycemic instability (30.8% vs. 24.8%), hypoglycemia (24.4%v vs. 18.4%), pregnancy (16.3% vs. 17.7%) and lifestyle of patients (14.5% vs. 13.5%).

For efficacy, the significant decrease of HbA1C between initiation and annual evaluation was similar in the two groups (8.4±1.6% vs. 7.7±1.1, p<0.0001 in asparte group and 8.5±1.5% vs. 7.8±1.1, p<0.0001 in lispro group).

For safety, the number of episodes of severe hypoglycemia per year decreased significantly between the start of CSII and annual evaluation in the two groups (0.3 vs. 0.13 per patient per year, p=0.0004 for asparte group and 0.27 vs. 0.14, p=0.009 for lispro group). No increase in ketoacidosis has been observed before CSII and during the last year of pump treatment (0.074 per patient per year vs. 0.066, p=0.8 for asparte group and 0.084 vs. 0.075 for lispro group).

When used in CSII, asparte insulin is as effective and as safe as lispro insulin. These two insulins used in pump provided better glycemic control, with less episodes of severe hypoglycemia and no increase of acidoketosis than multi injections.

2252-PO

Comparison of Incretin-Based Therapies: Liraglutide Offers Greater Improvements in A1c Than Sitagliptin or Exenatide across Baseline A1c Categories

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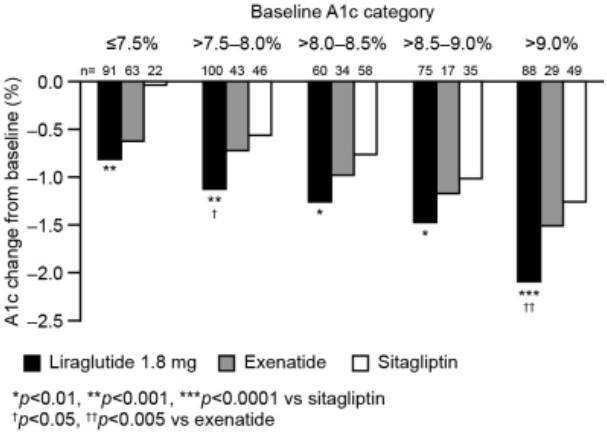
Several type 2 diabetes therapies demonstrate greater absolute A1c reductions in patients with higher baseline A1c. Treatment comparisons are a useful tool for physicians when selecting the most appropriate therapy for their patients, therefore a meta-analysis was performed to compare A1c reductions of three incretin-based therapies across a range of baseline A1c categories. Two phase 3 trials comparing liraglutide 1.8 mg once-daily with exenatide 10 μg twice-daily (both plus metformin [met] and/or sulfonylurea) and liraglutide 1.8 mg (+met) with sitagliptin 100 mg (+met) were included in this meta-analysis. Patients were arbitrarily split into five baseline A1c categories: ≤7.5%, >7.5-8.0%, >8.0–8.5%, >8.5–9.0%, >9.0%. ANCOVA analysis (LOCF ITT population) determined A1c changes from baseline to 26 weeks by baseline A1c category, with country and interaction between treatment and A1c category as fixed effects. All treatments improved glycemic control across every A1c category, with greater reductions observed at higher baseline A1c (Figure). Reductions ranged from 0.8% for liraglutide, 0.6% for exenatide and 0.05% for sitagliptin in ≤7.5% category to 2.1%, 1.5% and 1.2%, respectively, in >9.0% category. Liraglutide 1.8 mg offered significantly greater reductions in A1c vs sitagliptin across all A1c categories. Greater A1c reductions were observed with liraglutide vs exenatide in all A1c groups, reaching statistical significance in >7.5–8.0% and >9.0% categories. In summary, the general trend toward greater A1c reductions with higher baseline A1c was confirmed for all treatments. Regardless of baseline A1c category, liraglutide offered greater A1c improvements than exenatide or sitagliptin. This difference was apparent even in the lowest A1c category, particularly vs sitagliptin.



2253-PO

WITHDRAWN

2254-PO

Design and Preliminary Results of Veterans Inpatient to Outpatient Insulin Study

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Little data exists regarding optimal transition from inpatient to outpatient diabetes therapy. In inpatients with acute noncritical illness, the efficacy of basal-bolus insulin for treatment of hyperglycemia and the transition to pre-mixed insulin at discharge are being examined in a phase IV, randomized, open-label study of 120 patients with type 2 diabetes. During the inpatient phase, patients receive detemir and prandial aspart insulin titrated using our hospital-wide standardized insulin protocol. At discharge, patients are

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randomized to biphasic 70/30 NPH/regular insulin (Group A) or aspart analog 70/30 (Group B) twice daily. The 20 week outpatient follow-up consists of bi-weekly phone calls and monthly clinic visits utilizing glucose profiles to adjust therapy. At Week 16 visit, patients are transitioned back to pre-illness therapy or continued on their current insulin regimens based on provider and patient preferences.

Once 120 patients are enrolled, analysis will be done to determine which pre-mixed insulin is more effective. Results are reported of the first 40 patients enrolled with 3 screen failures, leaving an intention-to-treat cohort of 37 patients (all males, age 63 ± 8.4 y., BMI 30.5 ± 4.1 kg/m^2, duration of DM 12 ± 9.7 y). Eighteen were randomized to group A and 19 to Group B. Results of the initial cohort completing the study (groups A & B combined) are presented (mean + SD): initial HbA1c 9.2 ± 2.5%, plasma glucose (PG) 203 ± 97 mg/dl, inpatient insulin dose 0.33 ± 0.23 U/kg (52 ± 35 U). At hospital discharge, patients received a mean total daily dose (70/30 mix) of 0.54 ± 0.33 U/kg (65 ± 44 U). Of the 30 patients completing the entire study, the mean total daily insulin dose at 16 weeks was 0.67 ± 0.40 U/kg, representing a 24% increase since enrollment. Mean HbA1c and PG decreased significantly to 7.7 ± 1.4 (p=0.006) and 159 ± 46 (p=0.017), respectively. There was no significant change in body wt. Hypoglycemia incidence and treatment satisfaction scores were also analyzed.

The preliminary results from our study document the successful transition from inpatient to outpatient insulin therapy for patients with type 2 DM and acute medical illness.

2255-PO

Determinants of Glycemic Control among Participants in the BARI 2D Trial Treated with Insulin Sensitizers

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The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial with a 2-by-2 factorial design tested (i) prompt revascularization plus intensive medical therapy versus intensive medical therapy alone, and (ii) insulin-providing (IP) versus insulin-sensitizing (IS) therapy for a primary outcome of total mortality. Among 1155 participants in the IS arm, 955 had ≥ 3 year follow-up with the following characteristics (means): age 62 years, duration of T2DM 9.9 years, BMI 31.8 kg/m^2, hemoglobin A1C (A1C) 7.7%, 33% with prior MI, and 26% on insulin. Among the 955 participants, 335 (35%) had "good" glycemic control (GGC) defined as a mean A1C of < 7.0% and using only IS medications during > 80% of the follow-up period. From a multivariate logistic regression model based on these 955 IS patients, a number of baseline variables were identified as significantly associated with GGC. Baseline characteristics *positively* associated with GGC (odds ratio; 95% CI) included monotherapy with one IS drug versus not taking any IS drugs (2.4; 1.55-3.73), being from Brazil or Mexico compared to the US population (2.9 and 2.2; 1.67-5.04 and 0.95-5.18), moderate or strenuous exercise (1.72; 1.22-2.42), and fasting insulin level of > 5 micro IU/ml (1.53; 1.01-2.31). Baseline characteristics *negatively* associated with GGC include being on insulin (0.22; 0.13-0.37), being on metformin and a TZD versus not taking any IS drugs (0.30; 0.16-0.57), being from Vienna or Prague versus from the US (0.34; 0.12-0.92), serum creatinine >1.5 in males and >1.4 mg/mL in females (0.42; 0.19-0.94), current smoker (0.57; 0.34-0.97), high A1C (0.66 for each 1.0% increment; 0.59-0.74), and duration of diabetes (0.84 for each 5-year increment; 0.74-0.95). Odds ratios for BMI (1.07), waist circumference (1.02), serum triglyceride (TG) log scale (1.07), HDL 10 mg/dl increment (1.06), and TG/HDL ratio (1.15) were not significant (p>0.25 for all), and not part of the model. Attention to these significant characteristics may help predict whether IS therapy alone will be successful in maintaining an A1C of <7.0% for a prolonged period in patients similar to the BARI 2D cohort.

2256-PO

Determinants of Incident Diabetes Treatment: Evidence from Pan Asian Cohort Study

SUKYUNG CHUNG, ERIC WONG, BEINAN ZHAO, LATHA PALANIAPPAN, *Palo Alto, CA*

Early treatment of diabetes is the most cost-effective way to prevent complications. Despite recommendations, treatment of diabetes at its early stage may be suboptimal. We examined the likelihood of treatment for diabetes incidence in ambulatory care setting and how the likelihood differs by patient demographic and clinical characteristics. We extracted clinical and service data from the electronic health records (EHRs) for people in the Pan Asian Cohort Study, which uses EHR for Asian and non-Hispanic White (NHW) patients age≥35 years in a large mixed-payer, multi-specialty, multi-clinic ambulatory care organization. Incident type 2 diabetes was defined as evidence of diabetes (abnormal glucose values and/or physician diagnoses) in 2007-2009, after being under surveillance of 12 months diabetes free. We examined oral anti-diabetes medication prescriptions within six months of diabetes incidence as a treatment marker. Multivariate analyses included patient sex, age, race/ethnicity, insurance type, obesity, overweight, fasting glucose value, and main contraindications of oral diabetes medications. Physician-level clustering was adjusted. Significant results (P<0.01) are reported here. Of 901 patients identified as having incident diabetes, only a third (38%; n=345) were treated within six months of diabetes incidence. Significant positive predictors of treatment in multivariate analyses included Asian Indian (Odds Ratio (OR)=2.1; ref. category= NHW), obesity (OR=2.0), absence of kidney disease (OR=2.2), and higher level of fasting glucose (OR=1.02). In conclusion, incident diabetes is not as frequently treated as is recommended by clinical guidelines. Delayed medication treatment for patients with new diabetes is of concern and its rationale needs to be understood. Reasons for the more prompt treatment for Asian Indians merit further investigation. The higher likelihood of initiating a medication with higher fasting glucose level and/or a comorbidity (e.g., obesity) and the lower likelihood with a patient having a contraindicated condition (e.g., kidney disease) conform to evidence-based practice.

Supported by: NIDDK

2257-PO

Development of a Novel Assay To Measure Intact Glucose-Dependent Insulinotropic Polypeptide (GIP) Levels in Human Plasma

TSUTOMU HASHIMOTO, NAO WATANABE, TETSUYA UEDA, YUKIKO SHIMADA, DAISUKE YABE, YUTAKA SEINO, *Tokyo, Japan, Osaka, Japan*

Although the incretin hormones have attracted attention as bio-markers for drug development and clinical research in diabetes, a method to measure intact GIP levels has not been widely available. Here, we established a novel ELISA to specifically and efficiently measure intact GIP levels in human plasma.

The ELISA utilizes two antibodies (L41 and TB1093) specific to GIP established in our laboratory. L41 is a monoclonal antibody obtained from mouse hybridomas and is specific to N-terminus of human GIP (1-42), which is used as a catching antibody. TB1093 is a rabbit polyclonal antibody raised against C-terminus of GIP, is used as a detecting antibody. Our ELISA reacts with GIP (1-42), but not with GIP (3-42), GLP-1, GLP-2 and glucagon at all. The range of quantification, intra-reproducibility, inter-reproducibility and the stability during storage and repeated freeze-thaw cycles were assessed using human plasma samples which received solid-phase extraction prior to the ELISA. The quantification range of this method was 20 to 500 pmol/L. The CVs for intra-reproducibility and the inter-reproducibility were less than 10%. The recovery efficiency of spiked GIP into individual plasma was -3.95% to 3.20% relative to the theoretical values. Intact GIP in plasma was stable for 24 hours when stored at 4 degree, and 2 months when frozen at -20 degree. Intact GIP was also stable after 4 repeated freeze-thaw cycles. Human plasma samples from 28 healthy subjects and 30 patients with type 2 diabetes who were subjected to meal tolerance tests were analyzed by our ELISA after solid phase extraction. To compare levels of intact GIP to those of total GIP, the same plasma samples were also measured by a commercial ELISA (Millipore). Fasting levels of intact GIP and total GIP in healthy subjects were 7.15 and 10.5 pmol/L, and their postprandial levels were 22.1 and 74.8 pmol/L, respectively.

The current study indicates that our novel ELISA is specifically and efficiently measures intact GIP levels in human plasma, and our ELISA will be useful for clinical research related to diabetes.

2258-PO

Diabetes Duration and Efficacy and Safety of Glargine vs Comparators

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Disease duration (DD) is an important factor when evaluating treatment options for patients (pts) with type 2 diabetes (T2D). This analysis evaluated the effect of T2D DD on efficacy and safety outcomes in pts treated with glargine (GLAR) vs comparators (C).

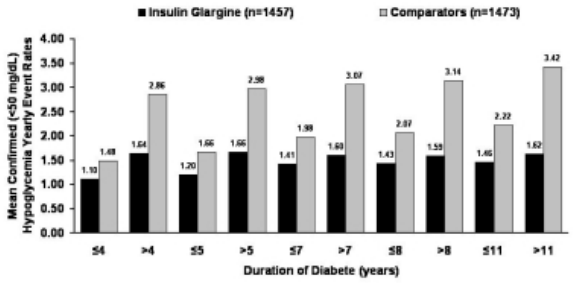
Pooled, 24-wk data from 9 prospective RCTs examined GLAR vs C (oral antidiabetic drugs, NPH, premix, lispro) in adults with T2D. In this analysis, patients (pts) were dichotomized by ≤7-y (n=1529) or >7-y (n=1401) T2D duration.

Of 2930 pts, 1457 received GLAR, 1473 C. Groups were similar at baseline (56.2% men; 83.5% white; mean age: 57.1 y, baseline A1C: 8.72%, DD: 8.6 y).

For author disclosure information, see page 785.

At 24 wk, GLAR reduced A1C more than C (-1.72% vs -1.54%), least squares mean diff $P<0.0001$. Significantly greater A1C reductions were seen for GLAR vs C, regardless of DD (all $P<0.0001$). Pts with DD >7 y had 47% greater odds of achieving A1C ≤7% with GLAR vs C ($P=0.0008$). Weight and BMI changes were similar by treatment and DD. The odds of a pt with DD >7 y experiencing at least 1 hypoglycemic event (BG <50 mg/dl) was approximately 30% lower with GLAR vs C ($P=0.0037$). Overall, pts on GLAR had lower yearly event rates of hypoglycemia (BG <50 mg/dl) vs C regardless of DD (Figure). Pts with DD >7 y had ~50% lower yearly rate of hypoglycemia (<50 mg/dl) with GLAR (1.31) vs C (2.75) ($P<0.0001$ for diff). For pts reaching A1C goal ≤7%, yearly event rates for hypoglycemia (BG <50 mg/dl) were similar with GLAR and C with DD ≤7 y; however, pts on GLAR and DD >7 y had significantly fewer events/y vs C ($P<0.0001$).

We conclude that use of GLAR in T2D had better A1C reduction and fewer hypoglycemic events than C regardless of DD.



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2259-PO

Differences in the Effect of Sitagliptin on 24-Hour Glycemic Variations in Japanese Type 2 Diabetic Patients Receiving or Not Receiving Sulfonylureas as Assessed by Continuous Glucose Monitoring (CGM)

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The effect of sitagliptin on 24-hour glycemic variations was compared in a total of 30 type 2 diabetic patients hospitalized for glycemic control (mean age, 69.9 ± 5.7 years; mean BMI, 25.3 ± 3.6 kg/m^2; mean HbA1c level [JDS value], 7.6 ± 1.3%; urinary C-peptide, 61.2 ± 36.5 µg/day).

The patients comprised 14 SU and 16 non-SU users of which 13 were on diet therapy alone, with the remaining 3 on insulin-sensitizers. Once stable glycemic control was achieved with diet therapy after admission, the patients were monitored for glucose levels for 4 days by CGM. The patients remained on the previous treatments on days 1 and 2 of CGM and were given sitagliptin 50 mg/day additively on days 3 and 4 of CGM.

The study revealed that despite no difference between the two groups in 24-hour mean glucose levels (mg/dl) (171.6 ± 34.4 vs. 163.2 ± 61.0), the SU users showed significantly higher values for the other parameters such as the SD of the 24-hour glucose levels, the total area for glycemic variation, and the MAGE. Sitagliptin led to significant decreases in mean glucose levels in both groups (SU users, from 171.6 ± 34.4 to 149.9 ± 26.7, $P < 0.05$; non-SU users, from 163.2 ± 61.0 to 146.7 ± 48.8, $P < 0.01$). Sitagliptin also led to decreases in the SD of the 24-hour glucose levels (mg/dl), the total area for glycemic variation, and the MAGE (mg/dl), with the decreases in these parameters except the MAGE found to be significant only in SU users.

A comparison of the baseline characteristics between the SU and non-SU users revealed that, despite similar mean 24-hour glucose levels, the SU users were associated with significantly greater glycemic variations than the non-SU users. Additionally, a comparison of the effect of sitagliptin between the two groups demonstrated that despite similar decreases in both groups in mean 24-hour glucose levels, the SU users were associated with greater improvements in parameters for glycemic variation than the non-SU users.

2260-PO

Discovery of Bi-Functional Peptides Balanced in Glucagon Antagonism & GLP-1 Agonism. A Search for the Molecular Basis in the Inversion of Activity at Homologous Receptors

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GLP-1 provides unique efficacy in the control of blood glucose in the treatment of adult-onset diabetes by enhancing insulin and partially suppressing glucagon secretion. It seems plausible that addition of glucagon-receptor antagonism to selective GLP-1 agonists would enhance glucose lowering. The identification of a dual-acting peptide functioning as an antagonist at the glucagon receptor and an agonist at the GLP-1 receptor constitutes a molecular challenge due to their structural homology. Our observations into the structure-activity, starting with glucagon/GLP-1 co-agonists demonstrate that N-terminal truncation to yield a specifically shortened analog fully antagonizes glucagon action while maintaining full GLP-1 receptor agonism. The chemical refinement of the position 6 amino acid in addition to backbone secondary structure stabilization by covalent lactam bond yielded a balanced dual-acting peptide individually characterized *in vitro* to possess an IC50 at the glucagon-receptor and an EC50 at the GLP-1 receptor of 20nM. The mixed-action peptide, when administered in mice, exhibited both activities and lowered blood glucose. The molecular basis for differential activity at two homologous receptors constitutes a conundrum and something worthy of structural definition. Homology analysis revealed a set of putative GLP-1 receptor sites where mutations were introduced to identify the source of differential activity. The initial results indicate that the core domain in each receptor determines the pharmacology. Separately, photoreactive peptides were synthesized and cross-linked to both receptors to site-specifically identify if these dual acting peptides maintain common sites for binding with native ligands.

Supported by: Marcadia Biotech

2261-PO

Drug-Drug Interactions of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, with Warfarin and Digoxin in Healthy Subjects

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Albiglutide (ALBI) is a long-acting GLP-1 receptor agonist in Phase IIIa development for the treatment of type 2 diabetes (T2DM). While ALBI is unlikely to cause drug interactions via cytochrome P450 induction/inhibition, GLP-1 and its analogs may alter the oral absorption and effects of co-administered drugs due to their ability to delay gastric emptying. Accordingly, the effects of ALBI on the oral pharmacokinetics (PK) of digoxin (DIG; 0.5 mg) and PK and international normalized ratio (INR) of racemic (R/S) warfarin (WAR; 25 mg) (agents commonly prescribed in subjects with T2DM) were assessed in independent, open-label, single-center studies. Healthy subjects received single doses of WAR (male, 18-55 years, 18-30 kg/m^2) or DIG (male/female, 18-55 years, 18-30 kg/m^2) alone and with steady-state ALBI exposure (50 mg ALBI by subcutaneous injection weekly for 5 weeks). Serial blood samples for PK were collected for each probe administered alone and when administered at steady-state C_{max} of ALBI. ALBI was well tolerated alone and in combination with each probe. ALBI did not significantly alter R/S WAR $AUC_{0-\infty}$ or C_{max}. ALBI did not significantly alter DIG $AUC0_{0-\infty}$; however, a small increase (11%) in DIG C_{max} was observed when co-administered with ALBI. T_{max} for R/S WAR and digoxin were increased from 1hr when administered alone to 1.5hr when co-administered with steady-state ALBI. These data suggest that potential gastric emptying effects of ALBI did not significantly affect the absorption profile of these probes. ALBI did not affect the INR profile of WAR (data not shown). In conclusion, there were no clinically significant interactions of ALBI on the PK of DIG or PK and INR of WAR.

Ratio of geometric LS means and 90% CI of the ratio of probes alone and with steady-state albiglutide.

Probe	N $AUC_{0-\infty}$ (Alone/Combo)	N C_{max} (Alone/Combo)	$AUC_{0-\infty}$ Ratio Combo:Alone (90% CI)	C_{max} Ratio Combo:Alone (90% CI)
R War	16/15	16/15	1.02 (0.98 – 1.07)	0.94 (0.89 – 0.99)
S War	16/15	16/15	0.99 (0.95 – 1.03)	0.93 (0.87 – 0.98)
Dig	25/21	30/24	1.09 (1.01 – 1.18)	1.11 (0.98 – 1.26)

2262-PO

Duration of Diabetes and Hypoglycemia Rates in T2D Patients Treated with Insulin Glargine vs NPH Insulin

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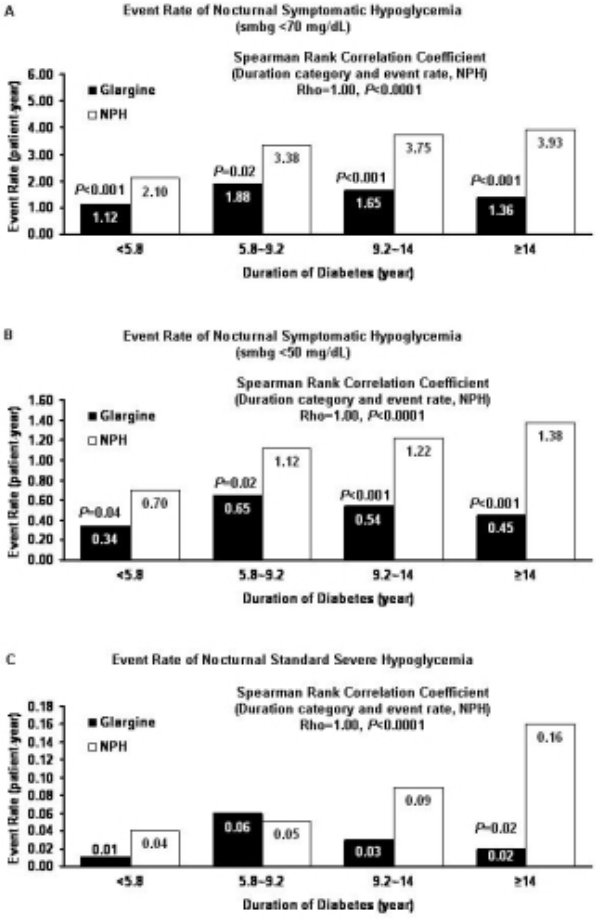
Recent ACCORD results suggest the incidence and risk of hypoglycemia increases with duration of type 2 diabetes (T2D). This analysis examined whether there were differences in hypoglycemia rates as a result of T2D duration in patients (pts) treated with glargine (GLAR) vs NPH.

Data were pooled from four 24-wk RCTs of insulin-naive T2D pts comparing GLAR + oral antidiabetic drugs (OADs) vs qd NPH+OADs. Pts were stratified into quartiles by T2D duration: <5.8 y (GLAR: n=378; NPH: n=285); 5.8-<9.2 y (n=330 and 269, respectively); 9.2-<14 y (n=289, 276); and ≥14 y (n=261, 242).

Of 2330 pts, 1258 received GLAR, 1072 NPH. Baseline demographics were similar except T2D duration in the highest quartile (GLAR: 19.64 y, NPH: 18.25 y; P=0.002). Despite similar or better A1C levels at endpoint for each quartile, GLAR pts had fewer episodes of nocturnal hypoglycemia (SMBG <70 mg/dl) vs NPH (P<0.05 for all). With duration increased, pts on GLAR had less nocturnal hypoglycemia at successively lower blood glucose (BG) cut-offs, eg, pts with T2D for ≥14 y had significantly fewer severe nocturnal hypoglycemic episodes defined as SMBG <50 mg/dl or <36 mg/dl despite a better endpoint A1C for pts with ≥14-y T2D duration (7.71% GLAR vs 7.93% NPH; P=0.031) with similar insulin dose (mean insulin dose GLAR vs NPH: 33 vs 34 U). Nocturnal hypoglycemia increased significantly only with NPH with increasing T2D duration (for NPH: SMBG <70 mg/dl, <50 mg/dl, and severe hypoglycemia; Rho (Spearman Correlation Coefficient)=1, P<0.0001 [Figure]).

We conclude that with longer T2D duration, pts taking GLAR had significantly less nocturnal hypoglycemia compared with NPH at successively lower BG thresholds.



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2263-PO

Effect of Caffeine on FFA Reduction by GS-9667 in Primary Adipocytes and SD Rats Treated with GS-9667

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GS-9667 is a partial agonist of the A_1 adenosine receptor (AR), which inhibits adipose tissue lipolysis and lowers circulating free fatty acid (FFA) levels. Caffeine, broadly consumed in the form of coffee or tea, is a non-selective AR antagonist and has been shown to increase lipolysis. Because caffeine could potentially counteract the effects of GS-9667, we explored the effect of caffeine on anti-lipolytic effects of GS-9667 *ex vivo* and *in vivo*. Adipocytes were isolated from male Sprague Dawley (SD) rats, treated for 1 hr with 1 nM-10 μM GS-9667 in the absence or presence of 10-120 μM caffeine, and lipolysis was measured. To complement our *ex vivo* studies *in vivo*, circulating FFA levels were monitored for 3 hrs in male SD rats which were given GS-9667 (5, 10 mg/kg, PO) in the absence or presence of caffeine (5, 10 and 20 mg/kg, PO). In isolated adipocytes, caffeine antagonized the inhibitory effect of GS-9667 on lipolysis concentration-dependently. EC_{50} for GS-9667 alone and in the presence of 10, 60, and 120 μM caffeine were 0.03, 0.06, 0.17, and 0.45 μM, respectively. In SD rats 5, 10 and 20 mg/kg caffeine concentration-dependently increased FFA by 2%, 26% and 44%, respectively. GS-9667 alone lowered FFA by 60% and 115% at 5 and 10 mg/kg. Caffeine at dose of 5 and 10 mg/kg (peak plasma levels: 30 and 60 μM) only partially and without significance antagonized the FFA-lowering effect of GS-9667 (10 mg/kg) by 18% and 25%, while 20 mg/kg caffeine (peak plasma level: 120 μM) significantly antagonized the effect of GS-9667 (10 mg/kg) by 65%. To determine the time-course of this interaction, 5 mg/kg caffeine, given at 30, 60 and 120 min before administration of 5 mg/kg GS-9667 inhibited the anti-lipolytic effect of GS-9667 by 36%, 25%, and 8%, respectively. Given the fact that most coffee drinkers generally take no more than 3-5 cups of coffee daily, equivalent to a peak plasma level of 30 μM achieved with 5 mg/kg caffeine, and that the plasma half-life of caffeine is ~2 hrs, our data suggests that caffeine intake is unlike to substantially impact the FFA-lowering effect of GS-9667.

2264-PO

Effect of Gender on Outcomes in Patients with T2D Treated with Insulin Glargine vs Comparators

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A pooled analysis of 9 clinical trials assessed the impact of gender on A1C, insulin dose, and hypoglycemia (hypo) in 2938 adult T2D pts (male=1651 [56.2%]; female=1287 [43.8%]) treated with insulin glargine (IG) (n=1462) or comparators (C) (n=1476; OADs, insulin [NPH, premix, Lispro] and diet). IG produced greater mean A1C reductions from baseline to wk 24 vs C (Table; P<0.0001) with a higher proportion of pts achieving A1C ≤7% (P<0.0001). IG pts needed lower weight-adjusted doses of insulin (IU/kg) than pts on C insulins (P<0.0001). Although the % of pts experiencing ≥1 symptomatic hypoglycemic event was similar for IG (58.5%) vs C (60.1%), the yrly event rate was lower for IG (P<0.0001). For confirmed hypo (BG <70 mg/dL), the % of pts experiencing ≥1 episode was similar across treatments, but the yrly event rate was lower for IG vs C (LSMD= –2.29; P<0.0001). In the combined cohort, males had a greater A1C reduction (P=0.04) while requiring lower insulin doses vs females (P=0.007). For IG patients, males had greater odds of reaching A1C ≤7% goal (P=0.02). Females had a greater likelihood of having ≥1 symptomatic hypoglycemic event and experienced a higher yrly event rate for symptomatic hypo vs males (LSMD = 1.3; P=0.014). Similarly, fewer males had ≥1 confirmed hypoglycemic event with BG <70mg/dL (OR=0.79; P=0.005); and males experienced fewer confirmed hypoglycemic events per year vs females (LSMD= –0.95; P=0.03). In conclusion, overall, IG improved glycemic control with lower risk of hypo vs C. However, compared to males, females had smaller reductions in A1C and were less likely to reach glycemic goal despite higher insulin doses and greater frequency of hypoglycemic events. Differences in gender responses should be considered when individualizing treatment plans for patients with T2D.

For author disclosure information, see page 785.

Parameter	IG vs C	Males vs Females[a]
A1C ↓ from baseline to week 24 (mean ± SD)	LSMD = −0.17% *P*<0.0001	LSMD = −0.07% *P*=0.04
Patients achieving A1C ≤7% (%)	OR=1.38 *P*<0.0001	OR[b]=1.32 *P*=0.02
Week 24 weight-adjusted insulin dose (IU/kg)	LSMD = −0.07 *P*<0.0001	LSMD = −0.03 *P*=0.007
Symptomatic hypoglycemia (≥1 event), % of pts	OR=0.92 *P*=0.31	OR=0.80 *P*=0.007
Symptomatic hypoglycemia, (events/yr)	LSMD = −2.6 *P*<0.0001	LSMD = −1.3 *P*=0.014
Glucose-confirmed hypoglycemia (<70 mg/dL; ≥1 event), % of pts	OR=0.90 *P*=0.17	OR=0.79 *P*=0.005
Glucose-confirmed hypoglycemia (<70 mg/dL) (events per year)	LSMD = −2.29 *P*<0.0001	LSMD = −0.95 *P*=0.03

LSMD = least squares mean difference; [a]For IG vs C comparisons, negative LSMD values and OR>1.0 favor IG while positive LSMD values and OR<1.0 favor C. For males vs females comparisons, negative LSMD values and OR>1.0 favor males while positive LSMD values and OR<1.0 favor females. [b]IG only.

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2265-PO

Effect of Intravenous Insulin on Glycemic Variability in Patients Hospitalized with Heart Failure

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Glycemic lability index (GLI), a measure of glycemic variability, has been associated with mortality in hospitalized patients with heart failure (HF). Multiple factors have been postulated to affect glycemic variability, but in patients with HF, route and method of insulin administration may be particularly important.

Hospitalized patients with diabetes and symptomatic HF were randomly assigned to intravenous (IV) insulin using a standard, nursing run protocol or subcutaneous (SQ) basal bolus insulin. Each group received subcutaneous rapid acting insulin dosed according to carbohydrate intake with meals. The glucose target was 100-150 mg/dl for both groups. A continuous glucose monitor (Ipro, Medtronic) was used to calculate mean sensor glucose, coefficient of variation (CoV), and GLI.

Of 25 patients, baseline characteristics were similar. In the first 24 hours of IV insulin, median glucose was modestly lower in the IV group (134 vs. 163 mg/dl, p=0.10). GLI, but not CoV, was significantly elevated in the first 6 hours of IV insulin (p=0.008 in the first vs the fourth 6 hour period), and stabilized thereafter. In the SQ group, CoV, but not GLI, increased significantly over the first 24 hours (p=0.01 in the first vs the fourth 6 hour period) and stabilized thereafter. After adjusting for mean glucose, body mass index, age, and duration of diabetes, IV insulin remained independently associated with significantly greater log transformed GLI and CoV at 6 hours.

The results show a transient early rise in glycemic variability with IV insulin compared to a delayed increase with SQ insulin in patients with HF exacerbation. Further study is needed to determine if this has an effect on outcomes.

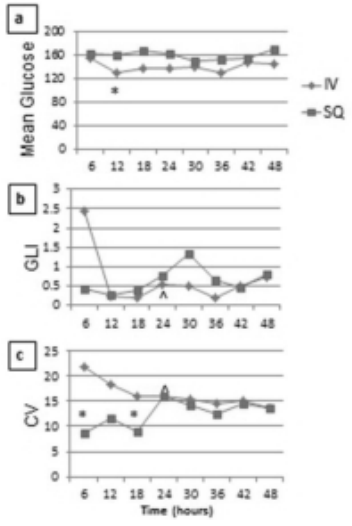

Figure: P<0.05 (*) between IV and SQ group, (^) from 6 to 24 hour within IV (b) or SQ (c) group.

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2266-PO

Effect of Multiple Doses of TAK-875 on the Pharmacokinetics of a Single Dose of Repaglinide

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TAK-875 is a highly selective GPR40 agonist that has demonstrated glucose-lowering effects in patients with T2DM by stimulating glucose-dependent insulin secretion. Repaglinide is an insulin secretagogue that acts by stimulating the release of insulin from the pancreas. The CYP-450 isozymes involved in the metabolism of repaglinide include CYP2C8 and CYP3A. TAK-875 inhibited the *in vitro* activity of CYP2C8 and has the potential to alter in vivo repaglinide clearance. This study was designed to evaluate the effect of multiple oral doses of TAK-875 on the pharmacokinetics (PK) of repaglinide.

This was a phase 1, open-label, sequential, single-site drug-drug interaction study. Fifty-two healthy subjects were enrolled in the study and received a single dose of repaglinide 0.5 mg on Day 1 followed by TAK-875 100 mg QD on Days 2 through 15. On Day 16, repaglinide 0.5 mg was also given with TAK-875. Administration of a single dose of repaglinide on Day 1 and 16 was followed by collection of PK samples for 24 hours. Repaglinide PK parameters were estimated using noncompartmental methods. The effect of TAK-875 was assessed by point estimates and 90% confidence intervals (CIs) of the ratios (Day 16 to Day 1) of the central values for repaglinide Cmax and AUCs using paired t-test.

Repaglinide was rapidly absorbed and eliminated following oral administration of a 0.5 mg dose alone or with TAK-875 100 mg; the median Tmax values were 0.5 hours on both days, and the mean T1/2 values were 1.2 and 1.3 hours on Day 1 and Day 16, respectively. Administration of TAK-875 100 mg with repaglinide 0.5 mg had no effect on the central values of the AUCs of repaglinide. The mean Cmax value of repaglinide when administered with TAK-875 was approximately 21% greater, and the 90% CI for the ratio of the central values of the Cmax (1.1306-1.2861) extended slightly above the no-effect range of 0.80 to 1.25.The increase in the mean Cmax value of repaglinide is unlikely to be clinically meaningful.

Co-administration of TAK-875 with repaglinide had little or no effect on the PK of repaglinide and multiple doses of TAK-875, with or without a single dose of repaglinide, were well tolerated.

2267-PO

Effect of the Once-Daily GLP-1R Agonist Lixisenatide on Gastric Emptying and Prandial Carbohydrate Utilization in Animal Models: A Comparison with Liraglutide

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It has been demonstrated that native GPL-1, as well as synthetic GLP-1R agonists, act *via* multiple mechanisms that synergistically result in improved blood glucose control, reduced appetite and food consumption, and weight loss. Secretion of GLP-1 in response to meals is significantly impaired in patients with type 2 diabetes. The current study in animals compares prandial responses to carbohydrate ingestion of two once-daily GLP-1R agonists, lixisenatide and liraglutide. The effects of lixisenatide and liraglutide were evaluated on gastric emptying in Wistar rats, in an oral glucose tolerance test in dogs, and in liquid meal tests in both normal C57BL/6J and diabetic db/db mice. Lixisenatide strongly and dose-dependently inhibited gastric emptying in rats with a significant effect already present at 1 µg/kg sc. However, even a 100 times higher dose of liraglutide was ineffective and significant inhibition of gastric emptying was observed only at doses of 500 µg/kg and above. In an oral glucose tolerance test in dogs, 1 µg/kg sc lixisenatide almost completely abolished blood glucose excursion. With liraglutide, the glucose-lowering effect during OGTT was significantly weaker than that of lixisenatide, even when liraglutide was administered at 50–100 times higher doses. After administration of a liquid meal (Ensure plus®), 3 µg/kg sc lixisenatide given to C57BL/6J mice was more effective in lowering prandial glucose excursions than 200 µg/kg liraglutide and 10 µg/kg of lixisenatide injected sc to diabetic db/db mice improved glucose tolerance at least as effectively as 200 µg/kg sc liraglutide. Therefore, we conclude that treatment with lixisenatide or liraglutide leads to differences in the prandial utilization of carbohydrates, with a stronger prandial effect shown for lixisenatide. The potent effect of lixisenatide on post-meal glucose control that was shown here might result, in diabetic patients, in pronounced effects on appetite, body weight, and thus improved glucose control so that more diabetic patients may reach their HbA_{1c} target.

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2268-PO

Effects of Canagliflozin on the Pharmacokinetics (PK) and Pharmacodynamics (PD) of Metformin and Glyburide

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Canagliflozin (CANA), an oral, potent, selective inhibitor of sodium glucose co-transporter 2, is being investigated for the treatment of patients with type 2 diabetes. Because CANA would be used with other antihyperglycemic drugs, its effects on metformin (MET) and glyburide (GLY) were assessed in separate studies. In the MET study, healthy subjects (N=18) received oral doses of MET 1000 mg on Day 1, CANA 100 mg qd on Days 4-7, and MET 1000 mg + CANA 100 mg on Day 8. In the GLY study, healthy subjects (N=29) received 1 dose of GLY 1.25 mg on Day 1, CANA 200 mg qd on Days 4-8, and 1 dose of GLY1.25 mg + CANA 200 mg on Day 9. In both studies, subjects ate a standardized breakfast within 10 minutes after drug administration. With CANA coadministration, 90% CIs of most PK parameters for MET, GLY, and GLY metabolites were within bioequivalence range (0.80-1.25); there was a small decrease (14%) in MET C_{max} (Table).

Analyte	Parameter	Geometric Mean Ratio[a]	90% CI
MET	C_{max}	0.86	0.73-1.01
	AUC_{∞}	0.97	0.82-1.14
GLY	C_{max}	0.93	0.85-1.01
	AUC_{∞}	1.02	0.98-1.07
3-cis-hydroxy-GLY[b]	C_{max}	0.99	0.91-1.08
	AUC_{∞}	1.01	0.96-1.07
4-trans-hydroxy-GLY[b]	C_{max}	0.96	0.88-1.04
	AUC_{∞}	1.03	0.97-1.09

[a]CANA + (MET or GLY)/MET or GLY alone; [b]GLY metabolites.

There were no notable changes in mean serum glucose or insulin levels with CANA + MET vs MET alone. Compared with GLY alone, CANA administered with GLY led to a small decrease in mean post-meal peak plasma glucose (15%), insulin (40%), and C-peptide levels (13%); led to a small decrease in mean insulin $AUC_{0\text{-}4h}$ (30%) and C-peptide $AUC_{0\text{-}4h}$ (9%); and had minimal effect on glucose $AUC_{0\text{-}4h}$. CANA alone and coadministered with MET or GLY was generally well tolerated. There were no clinically meaningful changes in clinical lab safety tests, vital signs, or ECGs, and no hypoglycemia. These results in healthy subjects suggest that (1) coadministration of CANA with MET did not result in clinically meaningful changes in MET PK or PD, and (2) coadministration of CANA with GLY did not result in significant changes in GLY PK and led to a small reduction in post-meal peak plasma glucose and to reductions in insulin and C-peptide levels.

2269-PO

Effects of Dapagliflozin on Patient Reported Treatment Satisfaction in Patients with Type 2 Diabetes Mellitus—Results from Two Double-Blind Trials

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Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a new treatment modality for type 2 diabetes mellitus (T2DM) which lower blood glucose by increasing urinary glucose excretion. Dapagliflozin (DAPA) is a first in class SGLT2 inhibitor in clinical development and has been shown to improve HbA1c and reduce weight, and is safe and well tolerated. However, its novel glucosuric mechanism of action warranted an evaluation of patient treatment satisfaction.

Patient-reported treatment satisfaction was measured utilizing the Diabetes Treatment Satisfaction Questionnaires for status (DTSQs max score 36) and change (DTSQc max score 18). Data were collected from two randomized, double-blind, multicenter, parallel group studies (N=1411), Study 4 (D1690C00004) and Study 5 (D1690C00005), in the DAPA phase III program. Study 4 was a 2-arm, 52 week study of DAPA up to 10 mg vs glipizide (GLIP) up to 20 mg, both added to metformin (N=814), and Study 5 was a 24 week study + 24 week extension of DAPA 2.5, 5 or 10 mg vs placebo (PBO), both added to glimepiride (N=597).

The overall DTSQs scores at baseline were high in all groups in both studies (>30 in Study 4, and > 27 in Study 5). In Study 4, the DTSQs showed a slight increase in both treatment groups at week 26. The DTSQc score at week 52 in Study 4 showed a higher mean value in the DAPA group (14.3 vs GLIP 13.6). In Study 5 at week 24, the DTSQs showed a slight increase in all groups and the DTSQc ranged from 13.2 to 13.6 in the DAPA groups vs 13.0 for PBO. At week 48, the DTSQs score improved further in all DAPA groups (mean change 3.5, 4.6, 4.4) vs PBO (2.2). In the single item measuring perceived frequency of hyperglycemia there was a noticeable reduction with DAPA compared with PBO at weeks 24 and 48.

The high level of treatment satisfaction maintained by patients in these 2 studies with ≥ 48 weeks of treatment suggests that dapagliflozin with its novel mechanism of action through glucosuria provides a well tolerated therapeutic option for patients with T2DM.

Supported by: AstraZeneca, Bristol-Myers Squibb

2270-PO

WITHDRAWN

2271-PO

Effects of Trial Enrollment on Metabolic Control in Subjects with Type 2 Diabetes: Is There a "Study Effect"?

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Reports suggest that study subjects will change behavior to improve diabetes control when participating in a clinical trial. This "Study Effect" could affect pharmacodynamic results. To assess whether there is a study effect in patients with Type 2 Diabetes (T2DM) enrolled in Phase I research trials, we compared metabolic and physiologic parameters at screening (SCR) and after admission (ADM) to an inpatient metabolic unit (prior to drug randomization).

We pooled data from 72 T2DM subjects in 3 Phase 1 clinical trials of novel hypoglycemic agents. Subjects were advised to maintain pre-enrollment diet, activity and medication prior to randomization to study drug or placebo. We measured body mass index (BMI), blood pressure (BP), fasting blood glucose (FBG), lipids (total cholesterol, LDL, HDL, and triglycerides (TRI)) and HbA1C in 30 patients. Fasting SCR values were compared to those at the time of ADM (1 or 2 days prior to randomization) by paired t-tests.

Results: Average time from SCR to ADM was 16.4 ±9.8 days (range 4-42 days).

	SCR(±SD)	ADM(±SD)	P value	N
BMI	31.3±0.7	31.4±0.7	0.50	72
BP (MAP)	95.6±9.6	94.4±11.5	0.40	72
TC	197±40	188±37	0.014	72
TRI	162±73	167±84	0.48	72
LDL	126±34	117±34	0.003	72
HDL	47±13	43±12	0.0008	72
FBG	155±34	174±38	<0.0001	72
HbA1C	8.0±0.7	8.1±0.7	0.27	30

*MAP: mean arterial pressure

While statistically significant changes were noted in some metabolic parameters, there was no evidence of improvement in diabetic control. Unexpectedly, FBG increased significantly for T2DM subjects in the screening window, despite advice to continue pre-enrollment diet, medication and exercise patterns.

Conclusion: No beneficial "study effect" could be observed. Study participation alone did not improve diabetes control and is unlikely to confound the ability to detect study drug effect in early clinical trials with diabetic subjects.

2272-PO

Efficacy and Safety in Patients Switched to an Insulin Glargine Plus Rapid-Acting Analog Basal-Bolus Regimen: The GLAD Study

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This observational study evaluated the efficacy and safety in daily practice in Hungary of patients with type 2 diabetes mellitus (T2DM) who switched to a basal-bolus regimen of insulin glargine plus rapid-acting insulin analog.

Efficacy endpoints were change in A1C, fasting and post-prandial blood glucose (FBG and PPBG) and body mass index (BMI) between enrollment and 6 months. The primary safety endpoint was incidence of severe hypoglycemic episodes. Treatment satisfaction was assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

A total of 1690 male and female patients were enrolled who were suboptimally controlled on a basal-bolus regimen of NPH insulin and regular

For author disclosure information, see page 785.

human insulin (A1C > 7%) and who had switched within the last 4 weeks to a basal-bolus regimen of insulin glargine plus a rapid-acting insulin analog. At enrollment mean (SD) age was 55.6 (12.7) years; BMI was 30.2 (5.4) kg/m^2. Patients had been treated for T2DM for 91.4 (82.3) months. FBG, PPBG and A1C at enrollment were 9.3 (2.3) mmol/L, 11.4 (2.8) mmol/L and 9.1 (1.4) %, respectively. Mean glargine and prandial insulin doses at enrollment were 27.0 (14.3) IU and 34.5 (15.4) IU, respectively. Following 6 months of therapy marked improvements in glycemic control were observed: Δ A1C, -1.6 (1.2) %; Δ FBG, -2.5 (2.3) mmol/L; Δ PPBG, -3.1 (2.8) mmol/L ($P < 0.001$, each). Glargine dose increased by 5.4 (6.9) IU, and prandial insulin dose increased by 2.7 (7.7) IU. The ratio of glargine to total dose increased from 43% to 46%. From enrollment to Month 3, ≥ 1 symptomatic hypoglycemic episode was experienced by 28.2% of patients. From Month 3 to Month 6, 22.9% experienced symptomatic hypoglycemia. During the same periods, severe hypoglycemic episodes were experienced by 3.1% and 0.8% of patients, respectively. DTSQ scores showed statistically significant improvements in all domains over the study period ($P < 0.001$).

In patients inadequately controlled on a basal-bolus regimen of NPH and regular human insulin, the switch to insulin glargine plus a rapid-acting insulin analog resulted in improved glycemic control without excess hypoglycemia.

Supported by: sanofi-aventis

2273-PO

WITHDRAWN

2274-PO

Efficacy and Safety of Linagliptin in Type 2 Diabetes Patients at High Risk of Renal Complications: Results from a Large Phase 3 Program

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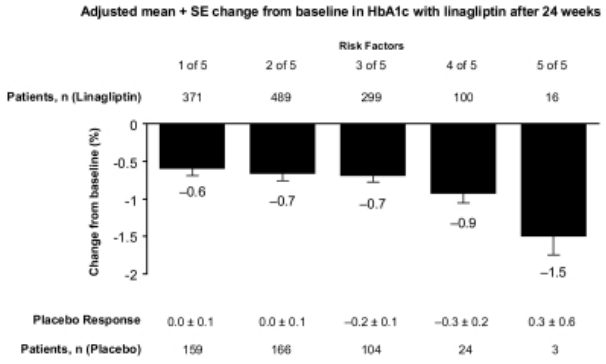
Type 2 diabetes mellitus (T2DM) is frequently associated with kidney damage and progressive renal impairment (RI). Renal risk factors include arterial hypertension, uncontrolled hyperglycemia, albuminuria, and existing RI. The novel dipeptidyl peptidase (DPP)-4 inhibitor linagliptin is excreted by a primarily non-renal route and is likely to be suitable for patients at risk of renal complications.

This pooled analysis of 3 randomized, placebo-controlled, Phase 3 clinical trials was conducted to determine the efficacy and safety of linagliptin in T2DM subjects at high risk of renal complications. Data were available for 2045 subjects, with 1731 having ≥1 renal risk factor.

Prevalence of renal risk factors was: 34% hypertension (≥140/90 mmHg) and 71% use of anti-hypertensive medication; 20% poor glycemic control (baseline HbA_{1c} >9%); 27% urine albumin/creatinine ratio >30 mg/gCrea; and 49% RI (glomerular filtration rate <90 ml/min/1.73 m^2). Outcomes were analyzed according to the number of risk factors present and results are shown in the figure below.



The mean adjusted changes from baseline in HbA_{1c} with linagliptin for patients with 1 to 5 renal risk factors were −0.6%, −0.7%, −0.7%, −0.9%, and −1.5% (all p<0.005 vs placebo), respectively. Linagliptin was well tolerated and the overall incidence of adverse events for linagliptin was similar to placebo (60.2% vs 58.5%).

In conclusion, early and effective treatment has been shown to prevent or delay progressive loss of renal function in T2DM. This is of particular importance in patients at high risk for renal complications. Linagliptin may provide an effective glycemic treatment option with the convenience of not having to adjust the drug dose even when there is a high risk of decline in renal function.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

2275-PO

Efficacy of Glimepiride/Metformin Fixed-Dose Combination Versus Metformin Uptration in Type 2 Diabetic Patients Inadequately Controlled on Metformin Monotherapy, a Randomized, Multicenter, Parallel-Group, Open Study in Korea

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The aim of this study was to compare the efficacy and safety of early combination therapy with glimepiride/metformin to metformin uptitration in reducing HbA1c levels from baseline over 24 weeks. A randomized, multicenter, parallel-group, open study was performed with arms of glimepiride/metformin (initial dosage 2/500 mg/day) and metformin uptitration (initial dosage 1,000 mg/day) in type 2 diabetic patients inadequately controlled by metformin monotherapy. Dosage was titrated to a maximum (8/2,000 mg and 2,500 mg, respectively) in order to reach the glycemic control goals (140~200 mg/dL of self monitored blood glucose without hypoglycemia). Serum hemoglobin A1c (HbA1c), fasting and postprandial glucose were measured for efficacy analysis. In all, 209 patients were randomized (glimepiride/metformin, n=101; metformin uptitraion, n=108). There was no significant difference in baseline characteristics between groups. At the end of the study, adjusted mean change in HbA1c level was significantly higher in the glimipiride/metformin group than metformin uptration group: -1.2% and -0.93%, respecvively (P<0.0001). A higher proportion of patients from the glimepiride/metformin group reached the goal of HbA1c<7% (73.3% vs. 46.2%; P=0.0002) and fasting glucose <140 mg/dL (83.3% vs, 68.1%; P=0.016). More patients experienced hypoglycemia with glimepiride/metformin (41% vs. 5.6%; P<0.0001) but there was no serious hypoglycemia in any group. Metformin had a beneficial effect on body weight (mean change from baseline – 0.72kg; between group difference -1.63 kg; P<0.05). Overall, both treatments were well tolerated and revealed similar safety profiles. This study demonstrated glimepiride/metformin fixed-dose combination therapy being more efficacious than metformin uptitration in type2 diabetic patients inadequately controlled by metformin monotherapy in Korea.

2276-PO

Efficacy of Treatment with a Basal-Prandial Insulin Regimen in Patients with Type 2 Diabetes Mellitus Previously Treated with Premixed Insulins

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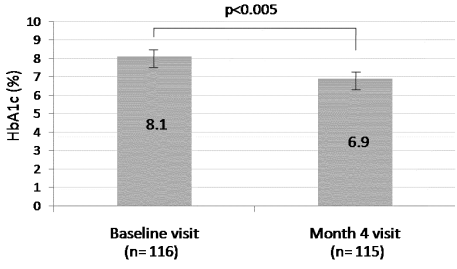
Aims: To assess whether basal-prandial therapy improves glycemic control in patients with type 2 diabetes mellitus (DM) with poor metabolic control (HbA1c>7%) treated with premixed insulins.

Methods: An observational, retrospective study in 116 patients with type 2 DM switched from premixed insulin to basal-prandial therapy. Demographics, anthropometrics, laboratory data, and data on antidiabetic treatment were collected from patients' medical charts at the start of basal-prandial therapy (baseline) and at month 4.

Results: HbA1c significantly decreased from baseline to month 4 (8.1±0.5% versus [vs] 6.9±0.7%;p<0.005) (figure 1), and 70 patients (60.9%) showed HbA1c≤7%.

Figure 1. Mean HbA1c values achieved during the study



HbA1c: Glycosilated hemoglobin

For author disclosure information, see page 785.

Fasting blood glucose (FBG) significantly decreased (175.4±31.2mg/dL vs 124.4±25.8mg/dL;p<0.005), as well as the number of patients with FBG<100 mg/dL (2 patients [1.7%] vs 21 patients [18.3%];p<0.005) and with postprandial blood glucose≤180mg/dL (14 patients [12.1%] vs 87 patients [76.3%];p<0.05). There were significant decreases in body weight (76.3±12.9kg vs 74.8±12.5kg;p<0.001) and waist circumference (96.1±16.0cm vs 94.4±14.5cm;p<0.005). Four patients (3.5%) showed hypoglycemia (2 asymptomatic and 2 symptomatic, and one of the latter occurred at night).

Conclusions: Switching from treatment with premixed insulins to a step basal-prandial therapy improved glycemic control in patients with type 2 DM, with a low incidence of hyperglycemia and a decrease in body weight.

2277-PO

Estimation of Basal Insulin Dose: Fixed 10 Units or 500/Correction Factor

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Usually basal insulin initiation dose is 10 U. Assessment of insulin sensitivity could be achieved by the measuring the fall in glucose from a single injection of rapid acting insulin represented as mg/dl/U, or correction factor, CF. From previous studies in T1DM patients, the total basal dose (TBD or total glargine dose) = ~ 500/CF. From a current study we post hoc evaluated a comparison between the TBD estimated to be a fixed 10 U and that estimated from 500/CF.

From 37 T1DM subjects the TBD was determined on a structured diet (isocaloric, 50% carbohydrate) with daily single meal omission using continuous glucose monitoring with daily downloads to adjust basal glucose to < 130 mg/dl but <10% under 70 mg/dl. The CF was estimated from the independently determined insulin to carbohydrate ratio, ICR, by the formula, CF = 4.5 x ICR. ICR was independently determined by adjusting the bolus dosing factors to achieve a 2-4th hour post-meal glucose to ± 20% of pre-meal glucose. Then the glargine dose was estimated by dividing '500' by CF. This dose deviation from the CGM titrated dose was compared to using a standard dose of 10 U. Significance was determined by the two tail paired analysis.

The 10 U fixed dose mean estimate exceeded the titrated TBD by 7.8 (10.4) U and the formula yielded a mean overestimate of 2.1 (6.9) U. The fixed dose estimate differed from the titrated TBD by ≥ 3 U in 30 (81%) and ≥ 6 U in 21 (57% (p = 0.00002). With the formula, 500/CF = TBD, the estimate was ≥ 3 U in 20 (54%) and ≥ 6 U in 8 (22 %) (p = 0.311).

In this retrospective evaluation of TBD estimation formulas, using 500/CF may result in a closer estimate of TBD than a fixed, 10 U. The CF may be estimated prior to beginning the basal insulin by monitoring the glucose fall by the injection of rapid acting insulin.

Supported by: Eli Lilly

2278-PO

Evaluating Benchmarking To Optimize Management of Type 2 Diabetic Patients: HbA_{1c} Control in the European OPTIMISE Study

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Diabetes complications markedly impact patient survival, quality of life and healthcare costs. Effective treatments and interventions reduce such burden and improve quality of care. Benchmarking (BM) incorporates 2-sided feedback of a physician's individual performance graded alongside the current mean achievement of a peer group, as well as patient's target attainment as regards major modifiable risk indicators. This study assessed the effect of BM on quality of care in type 2 diabetes outpatients over a 12 mo follow-up (FU) period. OPTIMISE was a non-interventional, observational study conducted in 6 European countries (NCT00681850). Physicians were randomly assigned to either a BM or control (CO) group. The primary endpoint was the percentage of patients achieving pre-set targets according to European guidelines (2007) for 3 major variables: HbA_{1c} (<7%), low-density lipoprotein cholesterol (LDL-C: <80 mg/dL [Belgium] <100 mg/dl [other countries]) and systolic blood pressure (SBP: <130 mmHg). The HbA_{1c} results are presented here. 2487 patients were randomized to BM and 1503 to CO by 368 investigators (229 BM, 139 CO). Both groups were highly comparable regarding all baseline demographic, anthropometric and diabetes-related parameters. 93.1% (3710/3986) of patients at baseline were taking medication(s) to treat diabetes, predominantly biguanides (76.5%, 2839/3710) and 94.1% (3278/3482) after 12 mo FU (biguanides 78.4%, 2571/3278). HbA_{1c} decreased in both groups after 12 mth FU: BM -3.99% (95% CI -5.04%; -2.94%), CO -3.49% (-4.87%; -2.12%). BM did not increase the frequency of patients achieving HbA_{1c} target after 12 mth FU vs. CO (58.9%, 1250/2124 vs. 62.7%, 846/1363). Unlike LDL-C (34.9%, 1350/3865) and SBP (27.2%, 910/3341), a majority (51.4%; 2052/3996) of patients at baseline had already attained HbA_{1c} target level. While the OPTIMISE results suggest that benchmarking did not have a positive effect on HbA_{1c} target attainment prevalence as single variable in unselected T2DM patients, the potential benefit of benchmarking needs to be investigated in subsets of patients not reaching HbA_{1c} target levels.

Supported by: AstraZeneca

2279-PO

Evaluation of Sliding-Scale Insulin Versus Basal-Prandial Insulin Use in Hospitalized Medicine Patients

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This study was conducted to determine whether use of basal-prandial insulin (BPI) regimens provide better glycemic control than conventional treatment with sliding scale insulin (SSI) in non-critically ill medicine patients when used in practice at a large university affiliated hospital. A retrospective chart review was performed of randomly selected non-critically-ill medicine patients with type 1 or 2 diabetes that received treatment with either hospital protocol SSI or BPI therapy with glargine and aspart. A total of 90 patients were included in this study and divided into a SSI group (n = 45) and a BPI group (n = 45). Blood glucose (BG) readings were compared between the two groups to determine which had the highest percentage of BG readings within a predefined goal range of 70-180 mg/dL. Patients in the BPI group had an average of 23.6 BG readings with 53.8% (mean of 12.7) between 70-180 mg/dL. Patients in the SSI group had an average of 26.1 BG readings with 66.7% (mean of 17.4) between 70-180 mg/dL (p = 0.07). Symptomatic hypoglycemia (BG < 60 mg/dL) occurred in 0.5 (2.1%) of the BG readings in the BPI group and 0.3 (1.2%) in the SSI group (p = 0.33). Hyperglycemia (BG > 180 mg/dL) occurred in 9.6 (40.7%) of the BG readings in the BPI group and 8.2 (31.4%) in the SSI group (p = 0.50).

Patients in this study showed no difference in glycemic control with the use of SSI compared to BPI therapy in the current practice model at this teaching institution. This finding is contradictory to previous studies comparing BPI with SSI and could be attributed to confounding factors, such as lack of standardization of dosing and titration of BPI. The results of this study should not diminish the current evidence and recommendations for the use of basal, nutritional, and correction dose insulin as the preferred means to manage inpatient blood glucose in non-critically-ill patients. These results should instead be used to make clinicians aware that despite their best efforts, current practices in this area may be inadequate outside of controlled settings.

2280-PO

Exenatide and Insulin Combination Therapy in Type 2 Diabetes

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Exenatide, a GLP1 analogue is licensed for use with oral agents for the management of type 2 Diabetes. Evidence for its use with insulin is limited but implies benefits in HbA1c reduction and weight loss. We aimed to assess its effectiveness on individuals with type 2 Diabetes, on insulin, at the Royal United Hospital between 2007-2010. This was a retrospective audit of all subjects initiated on exenatide, assessing the duration of treatment, weight reduction, and improvements in glycaemic control.

183 subjects were identified to be on exenatide of which 101 were on a combination of both insulin and exenatide whose average age was 58.2 yrs. Their mean duration of diabetes was 15yrs and their mean length on exenatide treatment was 10.5 months.

Baseline weight was 120.5kg, and HbA1c 9.4%. A constant reduction was noted in both measurements over the 12 month period following initiation. Weight changes were 120.6, 118.7 and 116kg with HbA1c readings of 8.7, 8.5 and 8.1% at 3, 6 and 12 months respectively.

Overall insulin requirements dropped from 135 to 114units.

78 individuals were on metformin in addition to insulin and exenatide. No significant dose changes were noted for any oral hypoglycaemic agents.

Exenatide was discontinued in 17 subjects, usually within the first six months. 4 subjects discontinued due to lack of response, 10 due to GI side-effects such as nausea, vomiting, and abdominal cramps and 3 for other reasons.

Exenatide therapy can be efficacious in weight reduction (-3.7%)and improving glycaemic control (-1.3%)when used in combination with insulin in type 2 Diabetes. Our group appear to experience less GI side-effects than in previous reports (10% vs. 35%).

For author disclosure information, see page 785.

2281-PO

Factors Associated with A1c Reduction in Asian Patients with T2DM: An Analysis of the FINE Asia Registry

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Asian patients with type 2 diabetes mellitus (T2DM) uncontrolled on oral antihyperglycemic drugs (OADs) were recruited from 11 countries in the FINE Asia registry. After 6 months of basal insulin therapy with or without concomitant OADs, there was marked improvement in glycemic control. The study included 2921 (50.3% female) patients, with a mean (SD) age of 56.4 (11.2) years and a T2DM duration of 9.3 (6.5) years. 2196 (75.2%) patients were prescribed insulin glargine, 637 (21.8%) NPH insulin, and 75 (2.6%) insulin detemir. Overall, A1C decreased from 9.8 (1.6) to 7.7 (1.4) % at Month 6.

This analysis aims to identify factors responsible for the A1C change using multivariate generalized linear model (GLM) regression where independent covariates included age, gender, initiating insulin type and other demographics and clinical characteristics related to diabetes management; $p < 0.05$ was considered statistically significant. In calculating P values, the statistical model factored the impact of different sample sizes.

2679 patients with A1C values at baseline and Month 6 were included. Initiating insulin with detemir (n = 61) vs glargine (n = 2016) was associated with less reduction in A1C (Δ = -0.50; 95% confidence interval [CI]: -0.17, -0.83; $P = 0.003$), as was initiating with NPH (n = 589) vs glargine (Δ = -0.36; 95% CI: -0.23, -0.49; $P < 0.001$). Older age was associated with greater reduction in A1C (Δ = 0.008; 95% CI: 0.003, 0.013; $P = 0.002$) as was a higher A1C value at baseline (Δ = 0.8; 95% CI: 0.77, 0.83; $P < 0.001$). Longer history of previous OAD usage was associated with less reduction in A1C (Δ = -0.026; 95% CI: -0.052, -0.0001; $P = 0.049$) as was female gender (Δ = -0.19; 95% CI: -0.06, -0.32; $P = 0.005$). There was no significant association of A1C reduction with baseline body weight, fasting blood glucose, blood pressure or insulin dose or with duration of diabetes.

Among patients with T2DM in Asia, the following factors were associated with greater A1C reduction: initiation of glargine vs NPH or detemir, older age, and higher A1C at baseline. Identification of these and other factors may support better glycemic control.

Supported by: sanofi-aventis

2282-PO

Factors Associated with Choice of Initial Insulin Regimen in People with Type 2 Diabetes: Baseline Findings from the A_1chieve Study

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The factors determining choice of insulin type and insulin regimen when starting insulin in people with type 2 diabetes remain unclear. Here we have used data from a large observational international study in 25 countries (A_1chieve) to evaluate the relationship between baseline clinical measures and the choice of basal, premix, mealtime or mealtime+basal insulin regimens in people starting insulin analogs in routine clinical practice. Data were available for 35 473 people with type 2 diabetes.

Choice of regimen varied between regions, such that 64% began with basal insulin in Latin America compared with 33% overall, while in south Asia 75% began with premix compared with 57% overall. Only a minority began with mealtime insulin alone (5%) or a mealtime+basal regimen (3%). After adjusting for regional differences, logistic regression showed that the number of oral glucose-lowering drugs (OGLDs), the prevalence of micro- and macro-vascular complications, glycated hemoglobin (A1C), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and body mass index (BMI) significantly influenced the choice of regimen while age, sex and duration of diabetes did not. People using ≥3 OGLDs and with higher A1C were more likely to start premix insulin, and less likely to start basal insulin (Table). People with micro- or macro-vascular complications or higher PPPG were also less likely to start with basal insulin, while in those on 1–2 OGLDs or with higher BMI, basal insulin was preferred (Table). In conclusion, choice of insulin regimen was significantly influenced by baseline use of OGLDs, presence of diabetes complications, A1C levels and BMI.

Table: Odds ratios for choice of basal vs non-basal insulin alone, and premix vs non-premix insulin. OGLD, oral glucose-lowering drug

	Odds ratio (95% CI)	
	Basal insulin alone	**Premix insulin**
n	11 729	20 150
Micro-vascular complications	0.92 (0.88; 0.96)	1.01 (0.97; 1.05)
Macro-vascular complications	0.91 (0.87; 0.95)	1.00 (0.96; 1.05)
1–2 OGLDs	1.10 (1.03; 1.16)	0.91 (0.86; 0.97)
≥3 OGLDs	0.85 (0.80; 0.91)	1.17 (1.09; 1.24)
A1C	0.96 (0.94; 0.99)	1.04 (1.01; 1.06)
FPG	1.02 (1.00; 1.03)	0.97 (0.96; 0.99)
PPPG	0.95 (0.94; 0.97)	1.00 (0.99; 1.02)
BMI	1.03 (1.02; 1.04)	0.98 (0.97; 0.99)

2283-PO

Factors Associated with Insulin Dose Change in Asian Patients with T2DM: An Analysis of the FINE Asia Registry

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Asian patients with type 2 diabetes mellitus (T2DM) uncontrolled on oral antihyperglycemic drugs (OADs) were recruited from 11 countries in the FINE Asia registry. After 6 months of basal insulin therapy with or without concomitant OADs, there was marked improvement in glycemic control. The study included 2921 (50.3% female) patients, with a mean (SD) age of 56.4 (11.2) years and a T2DM duration of 9.3 (6.5) years. 2196 (75.2%) patients were prescribed insulin glargine, 637 (21.8%) NPH insulin, and 75 (2.6%) insulin detemir. The mean daily insulin dose was 13.4, 10.9 and 15.6 U, respectively, at baseline and 15.4, 15.5 and 17.9 U, respectively, at Month 6.

This analysis tested the impact of factors on insulin dose change from baseline to Month 6 using multivariate generalized linear model (GLM) regression. Independent covariates included age, gender, initiating insulin type and other demographic and clinical characteristics related to insulin treatment; a $P < 0.05$ was considered statistically significant. When calculating P values, the statistical model factored the impact of different sample sizes.

2678 patients with insulin doses at both baseline and Month 6 were included. Initiating with NPH (n = 573) vs glargine (n = 1955) was associated with a greater increase in dose from baseline to Month 6 (Δ = 0.82 U; $P = 0.03$). An increase in dose was associated with higher body mass index (BMI) at baseline (Δ = 0.13 U per kg/m^2; $P < 0.001$), with higher baseline fasting blood glucose (FBG; Δ = 0.007 U per mg/dL; $P = 0.02$) and with higher baseline A1C (Δ = 0.22 U per A1C %; $P = 0.03$). A decrease in insulin dose was associated with age (Δ = -0.04 U per year; $P = 0.001$) and with baseline dose (Δ = -0.11 U per U; $p < 0.001$). There was no significant association of dose change with duration of diabetes, duration of OAD usage, blood pressure or gender.

Among patients with T2DM in Asia, the following factors were associated with greater increases in insulin dose after 6 months: initiating NPH versus glargine, as well as higher BMI, FBG and A1C. Identification of these and other factors may support more effective insulin titration.

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2284-PO

Glargine in Combination with an Oral Antidiabetes Drug in Patients with Type 2 Diabetes in Everyday Clinical Practice: Results from the LOAD Study in Russia

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The Lantus in combination with Oral Antidiabetes Drugs (LOAD) study was undertaken to evaluate insulin glargine in combination with sulfonylurea (SU) or metformin (MET) in everyday clinical practice among patients with type 2 diabetes mellitus (T2DM) in Russia.

The study was an open-label, prospective, observational study at 370 sites. Patients (>18 years old), whose physician decided to add glargine to their oral antidiabetic monotherapy, were eligible. Primary efficacy endpoint was change in mean A1C over a 3-month study period. Secondary endpoints included changes in fasting blood glucose (FBG), insulin dose, weight and body mass index (BMI) and number of documented symptomatic hypoglycemic episodes (HEs).

For author disclosure information, see page 785.

A total of 2500 patients were enrolled in the study. Data for 1855 and 1856 patients were available for analysis of efficacy and safety, respectively. Patients at baseline had a mean age of 58.3 ± 9.5 years and a mean duration of T2DM of 7.2 ± 5.4 years. Mean body weight was 83.4 kg and body mass index was 30.8 kg/m^2; 71.6% of patients were females. Glargine was used by 74.0% of patients in combination with SU and 22.3% in combination with MET. Mean A1C decreased from 9.6 ± 1.5% at baseline to 7.5 ± 1.2% at 3 months (P < 0.001). Target AIC <7% was reached by 32.5% of patients. Mean FBG decreased from 10.8 ± 2.5 mmol/L at baseline to 6.4 ± 1.2 mmol/L at 3 months (P <0.001). Mean daily glargine dose increased from a uniform starting dose of 10 IU to 22.6 ± 9.0 IU (median 20.0 IU) at 3 months. Mean body weight and BMI did not change. Symptomatic hypoglycemic and nighttime hypoglycemic episodes were experienced by 6.3% and 1.4% of patients, respectively.

The LOAD study provides evidence from everyday clinical practice in Russia that the addition of once-daily glargine to oral treatment improves glycemic control in patients with T2DM with low risk of hypoglycemia. The mean dose of glargine at 3 months was substantially lower than in randomized, controlled studies, suggesting that there may be additional potential for greater glycemic control.

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2285-PO

Glargine Utilization in Russia: A Retrospective Comparative Study To Evaluate Patients Switched from NPH Insulin to Insulin Glargine Compared with Patients Maintained on NPH

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The LAntus Utilisation in RUSsia (LAURUS) study was an open-label, retrospective, parallel-group comparative study undertaken at 1125 sites in Russia to evaluate the efficacy of switching patients with type 2 diabetes mellitus (T2DM) from NPH insulin to insulin glargine in real-life clinical practice. Eligible patients were those who had switched from NPH to glargine 3 to 6 months before the study but had maintained their oral antihyperglycemic drug (OAD) therapy or those who had taken NPH for 12 months without changes in OAD for ≥ 6 months. Primary efficacy end points were change in A1C over 3 months and percentage of patients reaching A1C < 7%. Secondary end points included changes in fasting blood glucose (FBG) and insulin dose and hypoglycemic episodes (HEs). Data were available for 6004 of the 10,000 enrolled patients. Patients who continued on NPH (n = 675) were older (60.5 vs 58.8 years) and had T2DM longer (11.0 vs 9.8 years) than those who switched to glargine (n = 5329). Mean BMI was similar (29.6 vs 29.7 kg/m^2). Mean baseline A1C was 8.9% in both groups. After 3 months of therapy, A1C decreased in the glargine group by 1.7 ± 1.4% versus 0.6 ± 1.2% in the NPH group (P < 0.001). Target A1C was reached by 41.9% of patients in the glargine group versus 12.4% of patients in the NPH group (P < 0.001). Mean baseline FBG was 9.5 ± 2.4 mmol/l in the glargine group and 9.4 ± 2.3 mmol/l in the NPH group. FBG decreased in the glargine group by 2.9 ± 2.3 versus 1.0 ± 2.2 mmol/l in the NPH group (P < 0.001). Mean change in insulin dose with glargine was 1.2 ± 8.5 versus 2.1 ± 5.5 IU with NPH (P < 0.001). Over the last month of the study, statistically significant differences favoring glargine over NPH were found for mean numbers of symptomatic HEs (0.12 ± 0.55 vs 0.39 ± 1.08; P < 0.001), nighttime HEs (0.11 ± 0.47 vs 0.59 ± 1.06; P < 0.001), and severe HEs (0.00 ± 0.06 vs 0.03 ± 0.21; P < 0.001). In Russian clinical practice, switching patients with T2DM inadequately controlled on NPH to glargine suggests improved glycemic control with less hypoglycemic episodes.

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2286-PO

GLP-1+Estrogen Conjugates: Enhanced and Selective Polypharmacology To Improve Diabesity

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Rodent and human clinical studies established that estrogen possesses anti-diabetic and weight-lowering actions resulting from combined effects in the pancreas, liver, and hypothalamus. Nonetheless, the clinical application of estrogen is limited due to the fear of its oncogenic potential and gynecological action. To enhance the therapeutic index of estrogen, we explored the preferential targeting of estrogen to desired tissues while minimizing action at breast and endometrial tissues through the use of incretin-based fusion peptides. By marrying the pharmacologies of GLP-1 and estrogen, we envision a constructive beneficial effect on glycemic and energy homeostasis by the combined insulinotropic and anabolic activities on pancreatic β cells with an anorectic effect at the hypothalamus. To explore each of the individual components' capacity for the regulation of metabolic parameters, a set of peptide-estrogen conjugates were synthesized to possess full GLP-1 agonism with a broad range of activities and with linker chemistries that enable differential estrogen release from chemical forms that are stable to other forms that fully release estrogen in a few hours. In preliminary studies in diet-induced obese mice, a fully active GLP-1 agonist with a stably-linked estrogen consistently proved to be more efficacious in improving blood glucose and body weight than the comparative GLP-1 control. The stable estrogen-peptide conjugates proved to be devoid of classical estrogenic activity as assessed by the lack of uterotrophic activity whereas labile estrogen-peptide conjugates displayed uterotrophic actions; however, the oncogenic potential in breast tissue is currently being explored. Chemical derivatives that reduced GLP-1 agonism and/or rendered the estrogen labile in plasma demonstrated lesser efficacy than the stable GLP-estrogen conjugates, suggesting the combined presence of GLP-1 and targeted estrogen are required to achieve the synergistic beneficial effects on metabolic outcomes; however, the mechanism by which these beneficial effects are achieved, particularly the tissues of action and estrogen receptors responsible, remains a focus of ongoing investigation.

2287-PO

Glucose-Lowering Effects of an Oral Glucokinase (GK) Activator, MK-0941, in Patients with Type 2 Diabetes (T2DM) Inadequately Controlled by Metformin

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MK-0941 is an orally active, selective, and potent allosteric GK activator. In a multicenter, randomized, double-blind, 4-week placebo-controlled study, the safety, pharmacokinetics and pharmacodynamics of MK-0941 when administered twice-daily before breakfast and dinner were assessed in patients with T2DM inadequately controlled with metformin. Patients (n=40) were required to be on a dose of metformin ≥ 1500 mg for at least 8 weeks with HbA_{1c} levels ≥ 7.0% and ≤ 11.0% prior to randomization. Patients received MK-0941 or placebo (PBO) in a 1:1 ratio. Administration was initiated at a dose of 10 mg and titrated every other day, based on pre-prandial glycemic criteria, up to a maximum dose of 60 mg MK-0941/PBO twice-daily. The dose achieved by Day 8 was continued through Day 28 of the study. Weighted mean glucose (WMG) concentrations were measured after a minimum of a week of stable dosing of MK-0941 (Day 13 of the study). The reduction in 24-hour WMG was greater than PBO (LS mean difference [90% CI] is 40.83 mg/dL [26.33, 55.32]). MK-0941 administration was continued up to 28 days to assess longer-term safety. The drug was well tolerated throughout the study: no consistent, clinically relevant, treatment-related adverse experiences were observed, and no patients discontinued treatment. In conclusion, in this ~4 week study, MK-0941 was well tolerated and associated with a statistically significant reduction in 24-hour WMG concentrations in patients with T2DM inadequately controlled with metformin. While these results appear promising, studies up to 30 weeks in duration demonstrated time-dependent loss of MK-0941 efficacy.

2288-PO

Gut Hypertrophy and L-Cell Proliferation in the Diabetic Zucker Fatty Rat

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The powerful effects of gastric by-pass on body-weight and glucose homeostasis have increased focus on the gut secretome as an important player in the resolution of type-2-diabetes (T2D). Gut hormones like glucagon-like-peptide 1 (GLP-1) and Peptide YY (PYY) released from the endocrine L-cell lining the lower part of the gastrointestinal tract (GI) has attracted much attention as both peptides are elevated following gastric bypass surgery. Previous studies have indicated an increased expression of preproglucagon and preproglucagon derived peptides in the Zucker diabetic fatty (ZDF) rat in both GI L-cells and in the brainstem preproglucagon expressing neurons. In light of these findings and because of a general lack of anatomical and morphometric analysis of the gut in T2D models we have performed an unbiased assessment of cellular and specific gene expression differences for future intervention studie. The GI-tract from 10 male Zucker diabetic fatty (ZDF) rats and 10 lean controls 20 weeks of age was immersionfixed in 4% PFA, embedded in agar and cut transversely using stereological sampling principles into 8-10 sections covering the duodenum, jejunum/ileum and colon, respectively. Thin paraffin sections where processed histochemically

For author disclosure information, see page 785.

to assess standard cellular differentiation, immunohistochemically to assess L-cell proliferation and by use of in situ hybridization (ISH) to assess changes in preproglucagon gene expression. ZDF-rats displayed increased plasma GLP-1 levels compared to control (10.6±1.7 lean vs 19.7+2.3 ZDF; GLP-1 pg/ml). The stereological assessment of gut volumes demonstrated a marked (250%) increase in mucosa volume as well as in total epithelial surface. Similarly, semi-quantitative ISH analyses demonstrated a near doubling of total preproglucagon expression related to a marked proliferation of preproglucagon expressing cells in the jejunum/ileum. In conclusion, we provide a stereological method to quantify structural changes (volume, surface area and cell numbers) in the gut and presents quantitative data demonstrating the high plasticity of the gut in response to metabolically disorders

2289-PO

WITHDRAWN

2290-PO

WITHDRAWN

2291-PO

Impact of a DPP4-Inhibitor on Liver and Heart Lipid Content and Cardiovascular Risk in Type 2 Diabetic Patients

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Background: Increased liver and cardiac fat are common in patients with type 2 diabetes mellitus (T2DM) and associated with increased risc for liver fibrosis and cardiovascular events. The effect of a DPP-4 inhibitor on the fat content of the liver and heart and cardiac functionhas not been evaluated.

Methods: 40 Patients, 20 male and 20 female, treated at our diabetes metabolic unit of the Medical University of Vienna with gliptins underwent magnetic resonance spectroscopy before and 6 months after start of therapy. MRT was performed with 3 Tesla Siemens MRT

Results: 40 patients have been included, 10 patients have finished the study (5 male, 5 female). The mean age was 55,9±7,2, weight 88,3±17, BMI 31,6± 5,1kg/m^2 and duration of diabetes 6±4 years. After 6 months mean weight loss was 5,1±2,3kg and -7±3 cm in waist circumference. Systolic and diastolic RR improved significantly: 151,3±2,6/94,2±10 mmHg to 122±14,4/80,1±8,9mmHg (p=0,04,p=0,05) respectively. HbA1c sunk significantly (8,3±1,5% to 6,5±0,4%, p=0,004). Before therapy patients had increased liver fat 15,3±9,1%, women significantly higher than men (30,2±2,5 vs 15,3±3,5, p<0,05) which significantly decreased in the 10 finished patients, p=0,0004, followed by a decrease of cardiac fat of 1,4±0,4%. The cardiac ejection fraction greatly improved (51,4±2,3 %to 67,1±0,5%, p<0,0001 as well as the myocardial mass decreased for 10,1±2,4 g.

Conclusion: DPP-4 inhibitors are very well tolerated an lead already after 6 months of therapy to significant decrease of liver and cardiac fat, improve the heart function, blood pressure and leas to weight loss where most of the other oral antidiabetics fail. These preliminary data could indicate gliptins as first line therapy of fatty liver with a special focus on cardiovascular function improvement.

2292-PO

Improvements in Metabolic Parameters along with Glycemic Status in Newly Diagnosed Obese North Indian Type 2 Diabetes on Liraglutide Addition to Metformin Monotherapy

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The incidence of Type 2 diabetes in the young is increasing rapidly in our part of world, with patients presenting with a myriad spectrum of biochemical abnormalities. Unmet pharmacological needs remain despite availability of different classes of antihyperglycaemic medications.

We included 39 patients (M:27, F:12) with newly diagnosed type 2 diabetes (according to ADA criteria), aged 23—38 years with an elevated BMI (according to Asian-Indian cut-offs) and elevated transaminases, on stable treatment with maximally tolerated doses of metformin for 3 months. Exclusion criteria included previous insulin treatment (except short-term treatment for intercurrent illness), previous exposure to liraglutide, and presence of macro- and/or microvascular complications and liver disease. Total body fat estimation was done by whole body DEXA. Informed consent was taken and the study was approved by hospital ethics committee. Liraglutide was initiated on the doses of 0.6mg s/c daily and uptitrated to 1.8 mg, along with reinforcement of diet and exercise. The patients were followed up at weekly interval for the first month, once every two week for next 2 months and once monthly for the remaining period.

Parameters	Baseline	3 Months	6 Months	*p*
Fasting/Post-prandial plasma glucose (mg%)	157±12/212±17	132±9/182±11	117±10/161±14	<0.001
HbA1c (%)	9.1±1.1	8.2±0.6	7.4±0.4	<0.001
Weight (Kg)	104±6	99±4.2	90±3.5	<0.001
SGOT/SGPT (IU/L)	72±7/62±8	52±5/42±6	27±3/22±7	<0.001
Triglycerides (mg%)	232±12	182±17	129±15	<0.001
HDL (mg%)	39±6	41±7	42±5	ns
LDL (mg%)	132±11	121±12	117±8	ns

At the end of 6 months, Liraglutide addition to metformin monotherapy in obese diabetes resulted in significant improvements in lipids, transaminases, weight and a reduction in total body fat alongwith improvement in glycemic control. Liraglutide was generally well tolerated with nausea being the initial complaint of the participants which resolved with continuation.

2293-PO

Influence of Baseline Glycemic Control on Sitagliptin-Induced Weight Loss in Patients with Type 2 Diabetes

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Improvement in glycemic control with antihyperglycemic agents has been associated with body weight (BW) gain, which may be related, in part, to reversal of glycosuria. However, treatment with metformin (MF) and GLP-1 agonists is associated with reductions in BW. Sitagliptin (SITA), a DPP-4 inhibitor, has been generally associated with small reductions or neutral effects on BW. As patients (pts) with low baseline (BL) A1C presumably have minimal potential for BW gain due to reversal of glycosuria, this analysis evaluated the influence of BL A1C on changes in BW with SITA. Results were obtained from 2 sets of pooled clinical trials: 5 trials of SITA monotherapy and 5 of SITA added to ongoing MF. Changes from BL in BW and A1C were assessed for the overall cohort and for subgroups based on BL A1C (≤7%

and >8.5%). Mean BL A1C was 7.9% (21% with A1C ≤7%; 25% >8.5%) in the pooled monotherapy cohort (N=1232). In this cohort, decreased A1C (0.7%) and BW (0.2 kg) were seen with SITA. BW decreased by 0.6 kg in pts with BL A1C ≤7% compared to an increase of 0.6 kg in pts with BL A1C >8.5%, associated with A1C decreases of 0.2% and 1.2%, respectively. Mean BL A1C was 7.8% (22% with A1C ≤7%; 19% >8.5%) in the pooled add-on to MF cohort (N=1426). In this cohort, decreased A1C (0.7%) and BW (1.1 kg) were seen with SITA. In contrast to the monotherapy cohort, BW decreased with SITA added on to MF by 1.3 and 1.1 kg in the BL A1C ≤7% and >8.5% subgroups, associated with reductions in A1C of 0.3% and 1.1%, respectively. Regression analyses found that BW change was negatively associated with BL BW and age and positively associated with female gender in both cohorts and positively associated with BL A1C in the monotherapy cohort. In summary, greater reductions in BW were observed with SITA monotherapy in pts with lower BL A1C. When added to MF, similar reductions in BW were seen with SITA regardless of BL A1C. The data suggest that physiologic increases in active GLP-1 due to DPP-4 inhibition with SITA lead to effects on BW that may be masked by improved glycemic control in monotherapy, whereas the effects on BW with SITA added to MF are not impacted by improved hyperglycemia.

2294-PO

Initial Treatment with Sitagliptin as Monotherapy or Combination Therapy Improves Markers of β-Cell Function in Patients with Type 2 Diabetes

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Incretin-enhancing therapies have been shown to improve markers of β-cell function, as reflected by increases in HOMA-β and decreases in the proinsulin/insulin (P/I) ratio. It is not clear, however, whether the combination of the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin (SITA) with other therapies such as metformin (MET) or pioglitazone (PIO) provide greater improvements in these markers than do SITA or these other agents alone. We examined change in HOMA-β and the P/I ratio in four clinical trials in which patients with type 2 diabetes were administered initial therapy for 12–24 weeks with SITA alone (100 mg qd), MET alone (1000 mg bid), the combination of SITA+MET (50 mg SITA bid + 1000 mg MET bid), PIO alone (30 mg qd), or the combination of SITA+PIO (100 mg SITA qd + 30 mg PIO qd). Results: Both HOMA-β and the P/I ratio consistently improved with SITA and MET monotherapies, whereas the effects of PIO monotherapy were inconsistent (HOMA-β) or inconclusive (P/I ratio) (Table). Improvements in both endpoints were generally greater when SITA was combined with MET or PIO than when the individual agents were given alone. These findings indicate that SITA alone or in combination with MET or PIO may improve β-cell function, and that the combination of SITA with MET or PIO appears to provide for greater improvement in markers of β-cell function (HOMA-β and the P/I ratio) than do the individual monotherapies.

	HOMA-β			Proinsulin/insulin ratio		
Treatment	n	mean baseline	LS-mean (95% CI) change from baseline	n	mean baseline	LS-mean (95% CI) change from baseline
Study 1:						
SITA	147	37.9	10.8 (4.8, 16.9)	114	0.435	−0.081 (−0.118, −0.043)
MET	154	44.8	14.3 (8.4, 20.3)	137	0.476	−0.121 (−0.155, −0.087)
SITA + MET	160	41.4	33.0 (27.2, 38.8)	157	0.487	−0.202 (−0.234, −0.171)
Study 2:						
MET	456	62.4	31.8 (20.7, 42.8)	458	0.518	−0.186 (−0.209, −0.162)
SITA + MET	465	50.5	54.6 (43.6, 65.5)	469	0.556	−0.238 (−0.260, −0.215)
Study 3:						
SITA	46	56.4	18.6 (1.2, 36.1)			
PIO	46	65.1	0.6 (−17.1, 18.3)			(n.d.)
SITA + PIO	43	52.1	27.8 (9.8, 45.8)			
Study 4:						
PIO	208	45.8	19.3 (8.7, 29.8)	204	0.418	−0.041 (−0.086, 0.004)
SITA + PIO	217	47.5	31.0 (20.7, 41.4)	213	0.467	−0.103 (−0.147, −0.058)

SITA, 100 mg/day sitagliptin; MET, 2000 mg/day metformin; PIO, 30 mg/day pioglitazone; LS = least squares; n.d. = not determined

2295-PO

Insulin Glargine vs Comparators in Adults <65 vs ≥65 Years of Age

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Due to the aging of the population, diabetes prevalence is expected to rise dramatically in older adults. A pooled analysis of 24-week data from 9 randomized controlled trials compared insulin glargine (IG) (used alone as basal insulin regimen) vs comparator (C) agents (OADs, insulin [NPH, lispro, premixed] and diet) in adults aged <65 years (n=1126 younger IG [YIG]; n=1137 younger C [YC]) and ≥65 (n=336 older IG [OIG]; n=339 older C [OC]) and also compared younger vs older adults for each treatment group. Compared with younger patients, those ≥65 years of age had significantly lower increases in weight, BMI, and insulin dose in both treatment groups, but no difference in likelihood of achieving A1C <7.0% or in A1C change and change in fasting plasma glucose (FPG). YIG and OIG patients were more likely to reach A1C <7.0% than YC or OC (YIG over YC, OR=1.317; OIG over OC, OR=1.506; $P \leq 0.01$). Significant reductions in A1C and FPG were seen in YIG vs YC and in OIG vs OC groups. For both age groups, insulin dose change was significantly lower with IG vs C. Hypoglycemia (hypo) rates did not differ between YIG and OIG patients. In contrast, any severe hypo was almost twice as likely in YC vs OC (OR=1.92, P=0.019), yet daytime hypo (self-monitored blood glucose <50 mg/dl) was less likely in YC vs OC patients (OR=0.76, P=0.049). Daytime and any hypo incidence and event rates were significantly lower with IG vs C in both age groups; there was no difference in nocturnal hypo. In conclusion, a basal insulin regimen with IG achieved better glycemic control vs C in both younger and older patients and was associated with a smaller increase in insulin dose and a reduced risk of daytime and any hypoglycemia. Compared with YIG, OIG patients achieved similar glycemic control with less increase in weight and BMI and lower insulin dose.

Table. Treatment Outcomes at 24 Weeks: YIG vs YC and OIG vs OC

Variable	IG	C	*P* Value (IG vs C)
Age <65 Years			
A1C <7.0% at endpoint, % patients[a*]	53.0	47.2	0.006
Adjusted ΔA1C, %[b†]	−1.67	−1.50	<0.001
Adjusted ΔFPG, mg/dl[b‡]	−76.70	−59.50	<0.001
Adjusted Δweight, kg[b§]	2.29	2.19	0.543
Adjusted Δinsulin dose, IU[b‖]	35.38	38.36[c]	0.034
Total hypoglycemia, SMBG <50 mg/dl, % patients	21.00	26.30	0.002
Daytime hypoglycemia, SMBG <50 mg/dl, % patients	16.82	21.11	0.007
Nocturnal hypoglycemia, SMBG <50 mg/dl, % patients	7.71	9.74	0.082
Age ≥65 Years			
A1C <7.0% at endpoint, % patients[a]	56.5	47.2	0.010
Adjusted ΔA1C, %[b]	−1.70	−1.55	0.020
Adjusted ΔFPG, mg/dl[b]	−81.34	−59.41	<0.001
Adjusted Δweight, kg[b]	1.62	1.60	0.960
Adjusted Δinsulin dose, IU[b]	19.65	30.63[c]	<0.001
Total hypoglycemia, SMBG <50 mg/dl, % patients	18.77	35.67	<0.001
Daytime hypoglycemia, SMBG <50 mg/dl, % patients	15.38	31.40	<0.001
Nocturnal hypoglycemia, SMBG <50 mg/dl, % patients	5.54	8.84	0.154

[a]Unadjusted data. [b]Adjusted for baseline.
[c]COMP includes NPH insulin, insulin lispro, and premixed insulin only.
YIG vs OIG: *P=0.331; †P=0.555; ‡P<0.079; §P=0.007; ‖P<0.001.

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2296-PO

Insulin Initiaition in Patients with Type 2 Diabetes Mellitus in Real-Life Practice in Italy—A Subanalysis of 1-Year Results from the CREDIT Study

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CREDIT is a 4-year non-interventional study, investigating the effects of long-term glycemic control with insulin treatment on the risk reduction of CV events associated with T2DM. People with T2DM who had recently started insulin (basal, short-acting, or premix insulin) were eligible for evaluation. In Italy, 417 people at 22 centers were included.

Results for the overall population (N = 3031) at 1 yr after insulin initiation have been reported. In the subanalysis for Italy (n = 387), 40% of people initiating with basal insulin had the same regimen at 1 year; the percentage

For author disclosure information, see page 785.

of people using basal + short-acting insulin increased from 25% at baseline to 40% Table. Mean dose at 1 year was 17.6 IU/d and 19.4 IU/d for patients using basal alone or basal + short-acting, respectively. For patients using premix or short-acting insulin alone, mean dose was 25.0 and 17.9 IU/d, respectively. Overall, mean A1C was reduced by 1.4%, and the percentage of participants with A1C £7.0% increased from 6% to 34%. Mean fasting blood glucose (FBG) decreased from 207.1 to 158.2 mg/dL, but 92.2% of participants had FBG ≥100 mg/dL. Hypoglycemic episodes were documented in 11.8% of participants.

Results from this 1-yr sub-analysis of the CREDIT study are encouraging, but the majority of patients remain above glycemic targets set by the ADA and EASD. High FBG and PPBG levels indicate suboptimal insulin dose titration over the first year.

	Baseline (n = 417)	1-y follow-up (n = 387)
Insulin regimen, %		
Basal alone	42.2	30.0
Basal + short-acting	24.9	39.8
Short-acting	11.8	3.9
Premix	7.4	8.5
Other	13.7	15.5
No insulin	0	2.3
A1C, %	9.1 (1.8)	7.7 (1.4)°
FBG, mg/dL	207.1 (69.7)	158.2 (47.4)°
PPBG, mg/dL	229.9 (68.5)	166.6 (57.9)°
Weight, kg	78.8 (15.3)	81.1 (15.6)°
Total cholesterol, mg/dL	187.9 (43.0)	181.4 (36.9)°
LDL cholesterol, mg/dL	113.9 (32.9)	107.2 (27.9)°
HDL cholesterol, mg/dL	48.3 (14.2)	48.2 (12.8)°
Triglycerides, mg/dL	155.9 (105.1)	152.1 (140.8)°

°On the basis of the data over the first year (n= 410)
Data are percent or mean ± SD except for insulin regimen.

Supported by: sanofi-aventis

2297-PO

Insulin Requirement Profiles in Short-Term Continuous Subcutaneous Insulin Infusion Therapy of Newly Diagnosed Type 2 Diabetic Patients

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Previous studies indicated that short-term intensive continuous subcutaneous insulin infusion(CSII) therapy in newly diagnosed type 2 diabetic patients could induce glycemic remission and β-cell function recovery. However, the initiation and titration of insulin dose was mainly based on experience. We therefore performed this retrospective study to investigate the insulin requirement profiles and its determined factors.

153 patients aged 20-75 years with newly diagnosed type 2 diabetes were enrolled. Baseline height, weight, fasting plasma glucose(FPG), post-prandial glucose(PPG), glycated hemoglobin A1c(HbA1c) and fasting insulin were measured. Insulin resistance (IR) and β-cell function were assessed with homeostatic model assessment (HOMA). CSII was applied in all patients for 2 weeks to achieve and maintain euglycemia (FPG 4.4-6.1mmol/L, PPG 4.4-7.8mmol/L). Insulin requirement profiles immediately after achieving euglycemia were recorded.

Euglycemia was achieved in 6.5±3.1 days. Total daily dose(49.3±16.6 IU), daily basal dose(17.7±5.8IU), and daily bolus dose(31.6±12.7 IU) were similar between genders. Total daily dose per kilogram of body weight (TDPK) (0.8±0.3IU/kg vs 0.7±0.2 IU/kg) and daily basal dose (18.7±5.7U vs 16.7±5.8U) was higher in patient with greater BMI (BMI≥25) than those with lower BMI (BMI<25). Basal and bolus dose accounted for 63.1±7.9% and 36.9±7.9% of total daily dose respectively. Bolus dose was assigned almost equally before breakfast, lunch and supper (1.1: 1.0: 1.0). TDPK was higher in women than men (0.8±0.3 IU/kg vs 0.7±0.2 IU/kg, P=0.017). After adjusting for age, genders and BMI, TDPK was associated with FPG, HbA1c, PPG, HOMA-IR and HOMA-B. Following formulas were established with linear regression models:

Female: TDPK = 0.833 + 0.039 × HbA1c + 0.012 × HOMA-IR + 0.017 × PPG - 0.032 × BMI (R^2=0.419);

Male: TDPK = 0.129 + 0.024 × HbA1c + 0.012 × HOMA-IR + 0.036 × FPG (R^2=0.168).

As conclusion, we suggest TDPK be estimated considering glycemic markers and insulin resistance status in the therapy. Insulin dose should be initiated with a basal-to-bolus ratio of 1:2, and by assigning pre-meal bolus equally.

2298-PO

Insulin Sensitivity May Predict Clinical Outcome with a GLP-1 Analogue

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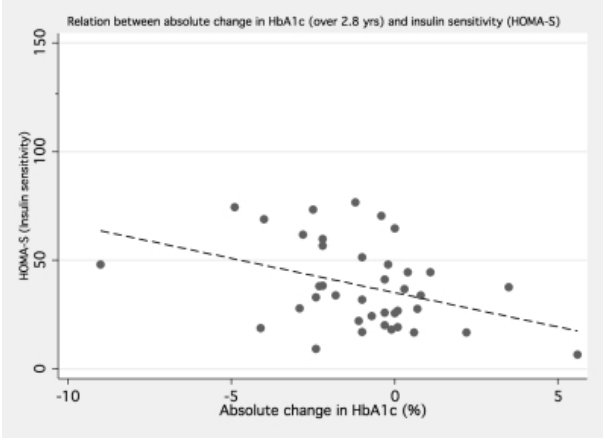
Exenatide, a glucagon-like peptide-1 (GLP-1) analogue, is an effective glucoregulator for treating overweight individuals not at target HbA_{1c} on maximum oral treatment. This prospective study aimed to determine whether beta cell function (HOMA-B) and insulin sensitivity (HOMA-S) predicts response to Exenatide treatment.

Prospective data on 43 type 2 diabetes patients (25/18 male/female) were collected over 2.8 years in primary care. HOMA-B and HOMA-S were measured prior to initiating Exenatide, with close monitoring of cardio-metabolic risk factors.

Mean (SD) age and BMI pre-treatment were 54.1±10.5 yrs and 35.7±7.5 kg/m^2 respectively. Despite no significant overall change in weight during follow-up, weight reduction correlated negatively with fall in HbA_{1c} (β = -0.51, p = 0.014). HbA_{1c} decreased (mean reduction 0.9%, p=0.04; p for trend = 0.01) in 61% of patients. Baseline HOMA-B was lower (36.1 vs 55.6, p=0.04) in subjects whose HbA_{1c} fell over time. In univariate analyses, HOMA-S as a measure of insulin sensitivity was inversely (β = -0.39, p=0.01; R^2= 0.15; Figure 1) and insulin resistance (IR) was directly (β= -0.43, p =0.007; R^2 = 0.18) related to change in HbA_{1c}, with no relation for HOMA-B. Thus greater decrease in HbA_{1c} was associated with higher baseline HOMA-S There was no relation at baseline between HOMA-S and HbA_{1c}.



Using mixed effects longitudinal regression including age, weight, LDL-C, HDL-C and triglycerides, change in HbA_{1c} (β=-4.0, p<0.0001) and HDL-C (β = -17.6, p=0.02) were independently associated with increasing insulin sensitivity (R^2 = 0.45).

Patients with greater measured insulin sensitivity achieve greater reduction in HbA_{1c} with Exenatide. Determination of insulin sensitivity may assist in guiding outcome expectation in overweight patients treated with GLP-1 analogues.

2299-PO

Insulin Treatment Improves Pancreatic Microvasculature in High-Fat-Fed and Streptozotocin Induced Diabetic Rats

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Our previous study showed early insulin therapy could induce glycemic remission and recovery of beta cell function in a proportion of type 2 diabetic patients. Since the pancreatic microvasculature is necessary for both islet growth and function, we observed the effect of insulin treatment on islets and vascular morphology in diabetic rats.

The SD rats were randomly assigned to NC (normal control, n=12), DM (diabetic rats ,n=12) and RI (diabetic rats treated with insulin, n=12). Diabetic rats were induced by high-fat diet and low dose streptozotocin (STZ). NPH insulin was given for 3 weeks initiated on the 3rd day after STZ injection in RI group. Intraperitoneal glucose tolerance test (IPGTT) was performed on the 3rd day after the end of treatment. Insulin treatment caused a decreased glucose area under curves (AUCs) and increased insulin AUCs during IPGTT. Compared to normal control, diabetic rats had less amounts and smaller sizes of the islets, which were ameliorated by insulin treatment.

For author disclosure information, see page 785.

The microvasculature in pancreas, showed through CD31 positive capillaries, was richer by insulin treatment. The expressions of Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2(VEGF-R2) in the pancreas were significantly increased.

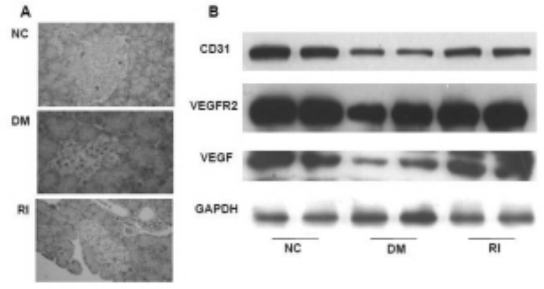

Fig. 1 A.Immunohistochemical localization of CD31 in pancreatic tissue. B. Effects of insulin treatment on CD31, VEGF and VEGF-R2 levels in Western blot in pancreas. NC: normal control, DM: diabetic group, RI: diabetic rats with insulin treatment

These results suggested that insulin treatment could ameliorate islet failure through increasing VEGF and VEGFR2 expression in the pancreas of high-fat fed and streptozotocin induced diabetic rats.

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2300-PO

Internet Based Program for Patient Specific Preoperative Management of Diabetes

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To simplify the complex preoperative/preprocedure management of the patient with diabetes, we developed an internet based expert system allowing providers to easily obtain patient specific recommendations for adjustments of any current diabetes medication, oral or injected. The perioperative management of diabetic patients presents special challenges as hypoglycemia needs to be avoided; uncontrolled hyperglycemia bears risks of electrolyte imbalances, perioperative infection and delays in wound healing. Preoperative diabetes management reflects the complex current outpatient diabetes management strategies that use any number of combinations of oral diabetes medications, long acting, rapid acting and premixed insulins, and new oral and injected incretin medications. Continuous infusion subcutaneous insulin pumps are now frequently utilized and need to be discontinued during longer procedures or in the presence of radiation.

Our group developed an easy to use reference system for providers to use during preoperative evaluation up to the day of surgery. By entering the basic information on any combination of diabetes medications, insulin regimens or insulin pumps and surgery parameters into a universally accessible, internet based expert system, providers can easily obtain patient specific recommendations for preoperative management. To facilitate communication, the system provides a handout or emails the patient with detailed recommendations. The program is available online under http://ucsf.logicnets.com.

Preliminary results of usability testing by 14 experienced providers on 22 preoperative and preprocedure (cardiac cath and interventional radiology) outpatients resulted in an evaluation time of 7.48 min. A direct improvement in the quality of care was recorded in 45% of patients, time savings in 66%. The software was considered helpful in 84% and easy to use in 90%. Recommendations were deemed acceptable in 87%.

Based on user feedback, the expert system continues to be modified and a formal randomized intervention trial is currently being established.

2301-PO

Italian LAUREL Study (Long-Acting Utilization in Real Life): Metabolic Effects of Changes in Basal Insulin Treatment in Patients with Type 2 Diabetes

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Randomized clinical trials have demonstrated the advantages of glargine compared with NPH in patients with type 2 diabetes mellitus (T2DM). We performed an observational study in a real-life setting to add information to these findings.

This Italian multicenter retrospective study evaluated the effects of switching from NPH to glargine (n = 496) versus continuing NPH (n = 500) in patients with T2DM. Primary end point was change in A1C 4 to 8 months after switch in the glargine group compared with change in the NPH group. Secondary end points were changes in fasting plasma glucose (FPG) and evaluation of safety data/cardiovascular risk factors. Covariates entered in the models were age, gender, duration of diabetes, age at diagnosis, duration of insulin therapy, variation of insulin dose, baseline A1C, baseline weight, and variation of weight.

Patients were caucasians, aged 68.5 ± 9 years, overweight (BMI 29.6 ± 4.9 kg/m^2), men 49.3%, with mean duration of diabetes 18.4 ± 9.4 years, most taking rapid insulin plus glargine or NPH. Switching to glargine significantly reduced A1C levels from 8.77 ± 1.39% to 8.18 ± 1.35% ($P < 0.001$); A1C levels increased slightly, from 7.86 ± 1.24% to 7.96 ± 1.38% (P = ns), in the NPH group ($P < 0.001$ for comparison between variations). FPG changed from 195.3 ± 61.4 to 171.9 ± 54.9 mg/dL ($P < 0.001$) with glargine and from 165.6 ± 53 to 167.3 ± 57.5 mg/dL (P = ns) with NPH ($P < 0.001$ for comparison between variations). Mean dose of basal insulin increased from 0.22 ± 0.10 U/kg to 0.26 ± 0.11 U/kg for glargine and remained stable for NPH (0.19 ± 0.09 U/kg to 0.20 ± 0.09 U/kg). There were no differences in vital signs, body weight, or waist circumference. Although reported in a minority of patients, hypoglycemias decreased slightly with glargine and increased with NPH.

In this Italian observational study, glargine was more effective than NPH at reducing A1C and FPG with less hypoglycemia. Glycemic control at the end of observation was inadequate in either group, highlighting the need for more effective titration in compliance with evidence-based guidelines.

Supported by: sanofi-aventis

2302-PO

LAPS-Exendin-4 Analog, a Novel Long-Acting GLP-1R Agonist for Weekly or Monthly Dosing in T2 DM Patients

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Exendin-4 analog is modified from of Exendin-4 which can elicit strong stimulation of human GLP-1 receptor via rapid dissociation rate, and is used for development of LAPS-Exendin-4. LAPS-Exendin-4 (HM11260C) is the chemical conjugate of proprietary Exendin-4 analog and recombinant human immunoglobulin Fc fragment (LAPS-carrier) through a non-peptidyl linker. LAPS-Exendin-4 is a sustained duration form of Exendin-4 analog based on the mechanism of decreased renal and vascular endothelial clearance.

Efficacy studies of LAPS-Exendin-4 in various animal models showed prolonged action as well as strong potency in HbA_{1C} reduction as well as in body weight reduction compared with natural form of Exendin-4. Pharmacokinetic studies in mice, rats, monkeys also demonstrated that LAPS-Exendin-4 is a sustained duration form, and the development of a long-acting GLP-1R agonist which can be administered up to monthly interval would offer a more convenient dosing schedule, likely enhancing patient compliance and ultimately clinical efficacy compared with conventional GLP-1R agonist therapies. The safety profiles of LAPS-Exendin-4 were evaluated in several studies including: single and repeat dose studies in rats and monkeys.

The LAPS-Exendin-4 was well tolerated from single dose escalation study in healthy volunteer and another dose escalation study in T2DM patients are ongoing to evaluate the effective dose level as well as PK/PD parameters.

2303-PO

Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER™) Trial: Rationale and Study Design

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Liraglutide is a once-daily human glucagon-like peptide-1 analog approved for use in patients with T2D. Although liraglutide is associated with significant reductions in fasting glucose, hemoglobin A1c, weight, and systolic blood pressure, its effect on cardiovascular (CV) outcomes is unknown. LEADER™ is an international, multicenter, randomized, double-blind, placebo-controlled trial designed to investigate the hypothesis that liraglutide is non-inferior to placebo, both in combination with standard of care, for a composite of major adverse CV events in patients with T2D. Approximately 9000 patients with T2D and at high CV risk will be enrolled in >30 countries. Eligibility criteria are

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listed below (Table). Patients are randomized 1:1 to once daily liraglutide 1.8 mg or placebo plus standard of care for 3.5–5 years. Assessments are being performed at enrollment, randomization, and every 6 months. The primary endpoint is time from randomization to an adjudicated composite outcome of CV death, non-fatal MI, or non-fatal stroke. The study is event- and time-driven and will not end until 611 events have accrued and a minimum duration of drug exposure has reached 42 months. Secondary outcomes include an expanded composite CV outcome, all-cause mortality, composite microvascular outcome (eye+kidney), foot ulcers, and various surrogate parameters for metabolic control and CV risk. Events will be adjudicated by independent committees blinded to treatment. Non-inferiority of liraglutide will be established if the upper bound of the 95%CI is <1.3. If non-inferiority is demonstrated, a test for superiority will be performed. The first patient was enrolled in September 2010; results are expected in 2016. LEADER™ is the first trial to test the long-term effects of liraglutide on CV outcomes in patients with T2D.

Inclusion criteria	Exclusion criteria
Type 2 diabetes	Type 1 diabetes
Age ≥50 years and ≥1 of the following: 1. Previous MI 2. Previous stroke or transient ischemic attack 3. Previous coronary, carotid or peripheral arterial revascularization 4. ≥50% arterial stenosis determined by angiography or other imaging of coronary, carotid, or lower extremities 5. History of symptomatic coronary heart disease documented either by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes 6. Asymptomatic cardiac ischemia documented by either positive nuclear imaging or exercise test or dobutamine stress echocardiography 7. NYHA class II or III heart failure 8. Chronic renal failure, defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 per Modification of Diet in Renal Disease (MDRD) or <60 mL/min per Cockroft-Gault formula	Use of glucagon-like peptide-1 analogs (exenatide, liraglutide, other) or dipeptidyl peptidase-4 inhibitors in the previous 3 months Use of insulin other than human NPH or long-acting insulin analog in the previous 3 months Acute decompensation of glycemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g., diabetes ketoacidosis) in the previous 3 months Acute coronary or cerebrovascular event in the previous 14 days Planned coronary, carotid, or peripheral artery revascularization NYHA class IV heart failure Current continuous renal replacement therapy End stage liver disease Malignant neoplasm requiring chemotherapy, surgery, radiation, or palliative therapy in the previous 5 years Familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma Current/planned pregnancy or non-use of adequate contraceptive methods
OR Age ≥60 years and ≥1 of the following: 1. Microalbuminuria or proteinuria 2. Hypertension and left ventricular hypertrophy by electrocardiography or imaging 3. Left ventricular systolic or diastolic dysfunction by imaging 4. Ankle/brachial index <0.9	
Anti-diabetic drug naïve or treated with ≥1 oral anti-diabetic drugs (OAD), human NPH insulin, or long-acting insulin analogue alone or in combination with OAD(s)	
Hemoglobin A1c ≥7.0%	

2304-PO

Liraglutide, a GLP-1 Receptor Agonist, May Be an Efficient Therapy of Obesity and Diabetes Associated with Prader-Willi Syndrome—Case Report

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Introduction: GLP-1 receptor agonists have been recently introduced for type 2 diabetes mellitus treatment. Two compounds, exenatide and liraglutide, have been registered. For the first time, we report a short term liraglutide use in a woman with morbid obesity and diabetes associated with Prader-Willi syndrome (PWS).

The female patient, aged 4 years, with typical features of PWS such as severe obesity (BMI - 32.6, BMI - SDS 9.8), developmental delay, hypotonia, and characteristic dysmorphic feature underwent genetic testing (DNA methylation analysis), which confirmed the clinical diagnosis. The patient was provided with behavioral treatment and growth hormone therapy; however, the results were not satisfying. Non-insulin-dependent diabetes mellitus was detected when she was 17 years old. Hypoglycemic treatment initiated by a pediatrician consisted of gliclazide modified-release 30 mg/day and acarbose 300 mg/day (metformin tablets were not tolerated). At the age of 18 years, the patient was then severely obese (BMI 65.2 kg/m^2) and had poorly controlled diabetes (HbA1c level - 7.8%). Insulin therapy in a multiple daily injection model was initiated. Over a period of 6 weeks she gained 2 kg and her HbA1c increased to 8.5%. We decided to switch her to liraglutide (1.8 mg/day) and powder metformin (1500 mg/day). Over the period of 14 week, we achieved a reduction of HbA1c level by 1.9% and of body mass by 3.2 kg. At the same time, her fat tissue amount decreased from 88.4 to 82.4 kg, as measured by biothesiometer and the waist circumference decreased from 141 to 133 cm. The treatment was well tolerated, no hypoglycemic episodes were observed.

In summary, liraglutide, in this case combined with metformin, may be an effective therapy in PWS patients with morbid obesity and diabetes. This is a potentially clinically important observation, particularly taking into account that the use of most anti-diabetic drugs inevitably leads to weight gain. However, the long term effects of such treatment in PWS subjects are uncertain, thus further studies on a larger number of patients are required.

2305-PO

Long Term Effects of Insulin Therapy with or without Addition of Oral Antidiabetic Drugs in Patients with Diabetes Mellitus Type 2

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An insulin treatment in patients with diabetes mellitus type 2 (DM2) is frequently necessary when monotherapy with oral antidiabetic drugs (OAD) does not lead to optimal therapy results. The aim of our study was to compare the effects of intensified insulin therapy alone with those of intensified insulin therapy plus OAD.

There were 119 patients with DM2 (mean age 69.8 years, mean BMI 27,6 kg/m^2 at the beginning of the insulin therapy) included in the study. In those patients the therapy goal (HbA1c < 7,0 %) could not be achieved under a monotherapy with OAD. The patients were divided in the following 2 groups: insulin therapy alone or insulin therapy together with OAD (Metformin or Pioglitazone or Acarbose).

Sixty two (62) patients were treated with insulin alone (mean duration of therapy: 115,2 months), 57 patients were treated with insulin plus OAD (mean duration of therapy 94,6 months). There were no significant differences in gain weight (insulin alone: 5,5 kg, insulin together with OAD: 5,8 kg). Furthermore, we found no differences in HbA1c values (insulin monotherapy: 7,18 %, insulin together with OAD: 7,36%). Also the daily dose of insulin units applied did not differ significantly between the two groups (insulin monotherapy: 63,8 international units/day, insulin together with OAD: 66 international units/day).

The results of our study show no improvement of glucose control when OAD are added to the intensified insulin therapy. Furthermore the gain weight and the total daily dose of insulin applied were the same in both groups. We can conclude that the addition of OAD does not improve the therapy results in patients with DM2 treated with insulin.

2306-PO

Long Term Use of Domperidone in Diabetic Gastroparesis

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Gastrointestinal (GI) disturbances due to autonomic neuropathy are common in type 2 diabetes (T2DM). Diabetic Gastroparesis is characterized by delayed gastric emptying in absence of mechanical obstruction of stomach. Cardinal symptoms are postprandial fullness, nausea, vomiting and bloating. Prokinetics are the mainstay of treatment and have been shown to improve symptoms and QOL. However, little data is available on their use beyond 8 weeks. The present observational study evaluated the efficacy and safety of long term domperidone use in diabetic gastroparesis

T2DM patients with gastroparesis who were on treatment with domperidone for more than 3 months were included in the study. Diagnosis of gastroparesis was based on presence of symptoms, abnormal tests for cardiac autonomic function, and a normal upper GI endoscopy. Clinical data was analysed for symptomatic improvement, side effects, loss of efficacy during treatment, and response to discontinuation.

The study group consisted of 61 T2DM patients, 32 men and 29 women, of 44 to 83 years. All had symptoms suggestive of gastroparesis, at least two abnormal tests of cardiac autonomic function (increased resting heart rate, abnormal E:I ratio, decreased 30:15 ratio, increased valsalva ratio, postural hypotension), and normal upper GI endoscopy. Average duration of treatment with domperidone was 22.88(±16.92) months (min 4, max 68 months). Twelve patients had stopped domperidone after 6–10 months due to non-efficacy, partial efficacy, or reluctance to take too many pills. No adverse effects were reported in discontinuation group. All the 49 patients(25 men, 24 women) continuing treatment reported improvement in symptoms. No side effects were reported or observed in these patients during follow up. Thirteen patients (3 men, 10 women) had discontinued domperidone for 2-14 weeks but restarted treatment due to recurrence of symptoms. All the patients on ongoing domperidone therapy continued to have symptomatic relief.

Our study shows that domperidone is effective in alleviating symptoms in patients with diabetic gastroparesis. Our results further show that long term use of domperidone for treatment of diabetic gastroparesis appears to be safe and effective.

2307-PO

Long-Term Glycemic Control in Patients Treated with Exenatide Twice Daily and Reduced Body Weight with 10 μg Exenatide: A 52-Week, Randomized, Phase 3 Study in Japanese Patients with Type 2 Diabetes Mellitus

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This multicenter study was conducted to assess the efficacy and safety of the GLP-1 receptor agonist, exenatide (E: twice daily [BID], sc) in Japanese patients taking oral antidiabetes including sulfonylurea with suboptimally controlled type 2 diabetes mellitus (T2DM). It consisted of a 24-week, placebo-controlled, double-blind trial (DBT) period and a 28-week, open-label extension treatment period with all subjects receiving exenatide. Baseline characteristics of 179 patients administered study drug at least once for 24-week DBT period (placebo 35; E 5 μg [E 5] 72; E 10 μg [E 10] 72) were as follows: 68% male; 58±10 y; BMI 25.5±4.1 kg/m^2; A1C (%) 8.6±0.9 (mean±SD). Of 144 patients in E 5 or E 10, 35 patients were discontinued mainly due to adverse events (eg, nausea). Results of the DBT period were previously reported. This analysis focuses on data from subjects treated by E in DBT period and continued on exenatide (64, E 5; 53, E 10) in the open-label extension period. The changes in A1C (%) from baseline observed at Week 24 persisted and remained dose-dependent at Week 52: -1.09±0.89 (E 5) and -1.59±0.98 (E 10). Dose-dependent changes in fasting blood glucose (mg/dL) also persisted at Week 52: -16.4±41.4 (E 5) and -29.8±39.0 (E 10). Similarly reductions in 7-point self-monitored blood glucose concentrations at Week 52 were comparable to those at Week 24. Clinically significant decreases in body weight (kg) from baseline were sustained in the E 10 group: -1.48±2.76 at Week24, -1.61±3.43 at Week52. Mild to moderate hypoglycemia and nausea were the most common treatment-emergent adverse events (TEAEs). During the 52 weeks, the incidences of hypoglycemia were 55.6% (E 5) and 61.1% (E 10), and those of nausea were 25.0% (E 5) and 37.5% (E 10). These incidences were similar to those in DBT period, suggesting the majority of TEAEs occurred in the first 24 weeks. Long-term exenatide treatment had a similar safety profile as observed in previous studies and was associated with improved glycemic control in Japanese patients with suboptimally controlled T2DM.

2308-PO

Lower Weight Gain and Better Outcomes in Patients with Type 2 Diabetes Starting Insulin Treatment When Baseline A1C<8.0%

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Weight gain is a commonly perceived effect of using insulin in T2D. We examined weight gain in the context of treatment efficacy and safety using pooled data from 9 randomized, controlled, clinical studies of adult patients with T2D. In each study, insulin glargine (IG) was tested against a comparator (C) (63% other insulins, 32% OADs, 6% dietary) over 24 weeks. Weight gain was assessed by treatment, demographics, age, and baseline A1C and FPG. The analysis included 2900 patients (IG: n=1449; C: n=1451) – 56% male, 84% white, mean (SD) age 57 (9.8) years, and T2D duration 8.6 (6.1) years. Mean weight gain was similar for IG-treated patients vs C (2.2 kg vs 2.1 kg). However weight gain was lowest in patients with baseline A1C <8%, rising with higher A1C. Results were similar for baseline FPG. Also patients ≥65 years gained less weight during treatment than younger patients and weight gain was significantly lower as a patient's age increased. More patients achieved A1C ≤7% with IG (58.3%) vs C (52.7%) (OR=1.27, *P*=0.0015). Trend analysis showed older vs younger patients treated with IG were more likely to achieve A1C ≤7% (*P*=0.0055); there was no such trend for C. Glucose confirmed (<50 mg/dL) hypoglycemia occurred less often with IG treatment than C, 1.5 vs 2.6 events/pt-yr, *P*<0.0001, with the lowest estimate among IG patients ≥65 years. In conclusion, weight gain with IG therapy is similar to that for C, but varies with patients' demographics. Starting patients when A1C <8% leads to better efficacy, comparable safety, and minimizes weight gain. Also patients ≥65 years show the lowest weight gain and highest odds of achieving A1C ≤7% with least hypoglycemia.

	Baseline		Week 24		Change from Baseline	
Age, years	IG Mean (SD)	C Mean (SD)	IG Mean (SD)	C Mean (SD)	IG Mean (SD)	C Mean (SD)
<50	96.9 (19.8)	98.3 (21.6)	99.9 (20.4)	101.2 (22.4)	3.0 (4.5)	2.9 (4.6)
≥50 to <65	91.1 (17.5)	91.0 (17.3)	93.2 (18.3)	93.1 (18.1)	2.1 (3.6)	2.1 (3.9)
≥65	85.0 (14.8)	84.3 (14.5)	86.5 (15.0)	85.8 (15.0)	1.5 (3.4)	1.5 (3.5)
Overall	90.9 (17.9)	91.2 (18.4)	93.1 (18.6)	93.3 (19.2)	2.2 (3.8)	2.1 (4.0)
			Pearson correlation (P-value)		-0.163 (<.0001)	-0.122 (<.0001)

	Baseline		Week 24		Change from Baseline	
Baseline A1C,%	IG Mean (SD)	C Mean (SD)	IG Mean (SD)	C Mean (SD)	IG Mean (SD)	C Mean (SD)
<8	89.5 (15.5)	89.7 (17.5)	90.8 (16.1)	90.8 (18.3)	1.3 (3.2)	1.0 (3.9)
≥8 to 9	90.0 (17.5)	91.1 (17.4)	92.8 (18.1)	93.2 (18.2)	2.0 (3.6)	2.1 (3.9)
≥9	91.9 (19.6)	92.3 (20.0)	94.9 (20.4)	95.2 (20.7)	2.9 (4.1)	3.0 (4.0)
Overall	90.9 (17.9)	91.2 (18.4)	93.1 (18.6)	93.3 (19.2)	2.2 (3.8)	2.1 (4.0)
			Pearson correlation (P-value)		0.195 (<.0001)	0.241 (<0.001)

Supported by: sanofi-aventis US

2309-PO

Marked Improvement in Glycemic Control with Exenatide (Byetta®) on Addition to Metformin, Sulfonylurea and Insulin Glargine in Type 2 Diabetes Mellitus

SABRINA PHILLIPS, NATALIE GULBRANSON, UDAYA KABADI, *Des Moines, IA*

The major effect of exenatide [EX] is attributed to lowering of post-prandial glycemia [PPG], whereas insulin glargine [GLAR] mainly improves fasting glycemia [FPG]. Therefore, we assessed effect of exenatide administration for 6 months on body weight [BW], daily insulin dose [INS], HbA1c and lipids. EX was initiated at 5mcg subcutaneously twice daily [BID] in obese subjects, BMI > 30kg/m^2, with C-peptide > 1ng/dL, and HbA1c 7.5-9.5%, while receiving metformin 2000mg daily, glipizide 40mg daily, and [GLAR]. Exclusion criteria were creatinine > 1.5mg/dL and liver enzymes > 2.5 times upper limit of normal. Initial 50 subjects, 48 men and 2 women, are included in this report. In 15 subjects, EX was discontinued within 1-3 weeks, 14 due to onset of nausea and vomiting, of which two also complained of abdominal pain, in whom amylase and lipase were elevated indicating presence of pancreatitis. One subject discontinued because of chest pain. In remaining subjects, EX was increased to 10mcg subcutaneously BID and continued. GLAR dose was adjusted at 6-8 week interval based on self monitored blood glucose readings. None of these subjects reported hypoglycemia requiring secondary attention. Results in then monitored subjects are shown in the table below.

	Pre-Rx	Post-Rx	p-value
Insulin (units/day)	105 ± 20	97 ± 23	>0.05
Body weight (kg)	133.6 ± 7.7	137.7 ± 8.1	>0.05
HbA1c (%)	8.2 ± 0.2	6.8 ± 0.1	<0.001
Total Cholesterol (mg/dL)	147 ± 11	128 ± 9	<0.05
Triglycerides (mg/dL)	278 ± 44	215 ± 40	<0.05
HDL (mg/dL)	38 ± 2	36 ± 2	>0.05
LDL (mg/dL)	79 ± 20	69 ± 8	>0.05

Therefore, exenatide may be an appropriate adjuvant option in obese subjects with Type 2 diabetes mellitus with lack of desirable glycemic control while receiving therapy with metformin, sulfonylurea, and GLAR.

2310-PO

WITHDRAWN

For author disclosure information, see page 785.

2311-PO

Modified Linjeta™ Formulations Reduce Local Injection Site Discomfort While Maintaining Ultra-Rapid Insulin Absorption Profiles

FRANK FLACKE, LORI BLANCHFIELD, PHILIP PICHOTTA, SOLOMON STEINER, ALAN KRASNER, *Danbury, CT*

Linjeta™ is a formulation of recombinant human insulin which is absorbed more rapidly than regular human insulin and insulin lispro. Previous studies performed with a prototype formulation of Linjeta (25 U/ml, pH 4) have shown an association with local injection site discomfort, particularly at the outset of treatment. Modifications of the Linjeta formulation designed to optimize toleration have previously been shown to have similar ultra-rapid absorption profiles. This report summarizes two studies in which discomfort associated with subcutaneous injections of these modified formulations was evaluated. In both studies, a 100 mm visual analog scale (VAS) where 0 represents no discomfort and 100 represents the worst possible discomfort were used to characterize blinded test insulin injections. The first study was a randomized, crossover trial comparing discomfort associated with injections of the Linjeta 25 U/ml (VJ25) prototype formulation vs. Linjeta 100 U/ml, pH7 (VJ7) and insulin lispro in 54 patients with type 1 diabetes. VJ25 and VJ7 resulted in VAS scores (mean±SE) of 22.0 ± 2.8 and 17.3 ± 2.5 (p = 0.041 for difference between Linjeta formulations), respectively, compared to a score of 5.3 ± 1.0 for insulin lispro. The mean qualitative severity ratings were in the mild range or lower for all three study drugs. In the second study, 13 subjects with type 1 diabetes received injections of the previously studied 100 U/ml Linjeta formulation (VJ7) and two modified 100 U/ml formulations (BIOD-102 and BIOD-103) which have different concentrations of the same or similar excipients. BIOD-102 and -103 received VAS scores (mean±SE) of 4.0 ± 1.2 and 9.0 ± 2.6 respectively compared to a score of 20.6 ± 6.7 for VJ7 (p = 0.028 and 0.112 for difference between BIOD-102 and -103 respectively and VJ7). The mean severity ratings were in the mild range for all three formulations and were significantly improved for the two modified formulations. In conclusion, formulation modifications of Linjeta result in preserved ultra-rapid insulin absorption with improved local toleration more similar to that seen with lispro.

2312-PO

WITHDRAWN

2313-PO

One-Year Liraglutide Treatment Offers Greater Weight Reduction and More Improved Glycemic Control Compared with Sitagliptin, Both in Combination with Metformin

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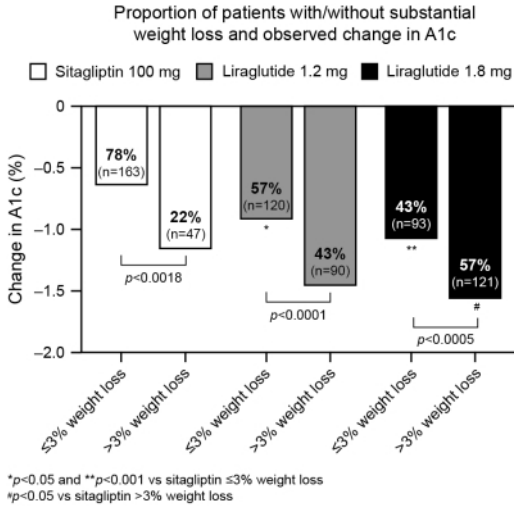
Glucagon-like peptide-1 (GLP-1) receptor agonists can promote weight loss whereas DPP-4 inhibitors are generally weight-neutral. A post-hoc analysis of a 26-week randomized trial has shown that once-daily liraglutide (LIRA) at 1.2 mg and 1.8 mg on a background of metformin resulted in significantly greater A1c reductions in patients with bodyweight (BW) loss of >3% vs ≤3%. A1c reductions were greater following treatment with LIRA in both weight-loss groups compared with sitagliptin 100 mg/day (SITA), also on a background of metformin. We report the results from this post-hoc analysis following a 26-week extension of this randomized trial. Patients continued treatment to which they were originally randomized. 497/554 (90%) of completers from the initial 26-week study entered the 26-week extension phase. After 1 year's treatment, weight reductions in the total study population were significantly greater for LIRA 1.2 mg and 1.8 mg than SITA (-2.8 kg and -3.7 kg, vs -1.2 kg, respectively; p=0.0001). Patients who lost >3% BW had significantly greater reductions in A1c compared with those who lost ≤3% BW in all treatment groups (Fig). Within each weight-loss group, treatment with LIRA 1.8 mg led to significantly greater reduction in A1c vs SITA, and in the ≤3% weight-loss group LIRA 1.2 mg led to a significant reduction in A1C vs SITA. The proportion of patients achieving ADA target A1c<7.0% was significantly greater with LIRA 1.8 mg in both groups vs. SITA and for 1.2 mg in the ≤3% group vs SITA. In conclusion, 1 year's treatment with LIRA or SITA resulted in significantly greater reductions in A1c in patients who achieved weight loss of >3%. Importantly, A1c reductions were significantly greater following 1 year's treatment with LIRA 1.8 mg compared with SITA regardless of the weight loss achieved.



2314-PO

One-Year Liraglutide Treatment Reduces A1c to a Greater Extent Than Sitagliptin, Both in Combination with Metformin, Independent of Baseline A1c Levels

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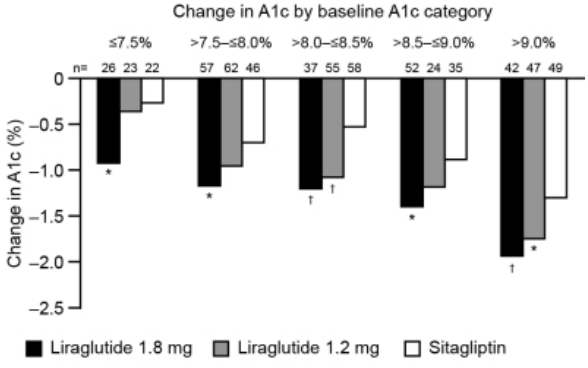
Baseline A1c is an important factor in therapy choice and also influences magnitude of response to treatment. A 26-week randomized trial previously has shown that in comparison with sitagliptin 100mg/day (SITA), liraglutide (LIRA) once daily (1.2 mg and 1.8 mg) produced greater reductions in A1c. Furthermore, a post-hoc analysis showed that at the highest (>9.0%) and lowest (<8.0%) baseline A1c, both doses of LIRA were more effective at lowering A1c than SITA. We report a similar post-hoc analysis following a 26-week extension of this randomized trial, in which patients continued treatment to which they were originally randomized. Five baseline A1c ranges were used to categorise patients (see Figure). Over 52 weeks, LIRA (both 1.2 and 1.8 mg) and SITA improved glycemic control across all baseline A1c categories, with greater reductions at higher baseline A1c levels (LS means from ANCOVA). Reductions in A1c across baseline categories ranged from 0.3–1.3% for SITA, 0.4–1.8% for LIRA 1.2 mg, and 0.9–1.9% for LIRA 1.8 mg. End of treatment A1c ranged from 7.1–8.2% for SITA, 6.9–7.8% for LIRA 1.2 mg, and 6.4–7.6% for LIRA 1.8 mg. LIRA 1.8 mg reduced A1c more successfully vs SITA (all categories: p<0.05). LIRA 1.2 mg reduced A1c more successfully vs SITA in two baseline groups: >8.0–≤8.5% (p=0.005) and >9.0% (p=0.03). There were no significant differences between LIRA 1.2 mg and LIRA 1.8 mg in any baseline A1c category. Nausea was initially higher with LIRA (1.2 mg, 21.7%; 1.8 mg, 27.5%) than SITA (5.5%). Minor hypoglycemia (episodes/patient/year) was similar for LIRA 1.2 mg (0.143), 1.8 mg (0.154) and SITA (0.137). In conclusion, LIRA more successfully reduced A1c than SITA across a broad range of baseline A1c values.



ADA-Funded Research

For author disclosure information, see page 785.

2315-PO

Oral Glucose-Lowering Drugs in Relation to Initial Choice of Insulin in Different Parts of the World; Findings from the A_1chieve Study

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When beginning an insulin regimen in type 2 diabetes, people with diabetes have a choice of insulin types and combinations, and a choice of oral glucose-lowering drugs (OGLDs) to be used concurrently. Here we have reviewed current practice across Asia, Africa, Europe and Latin America in 66 726 participants from 28 countries enrolled in the A_1chieve study. This is an open-label, multinational, observational study of people starting insulin detemir, insulin aspart (with and without any basal insulin) and biphasic insulin aspart in routine clinical practice. Baseline data for 36 810 previously insulin-naive people are reported to assess OGLD use when starting insulin. Baseline A1C in the basal, mealtime, and premix insulin groups was 9.5 %, but higher (10.0 %) in those beginning a mealtime+basal regimen. Duration of diabetes was similar for people starting mealtime (7.2±5.7 yr) insulin alone or premix (7.9±6.0 yr), but longer for those starting basal alone (9.4±6.7 yr) or mealtime+basal (10.0±6.4 yr) insulin regimens. Metformin was continued in ~70% of people, except those starting a basal–bolus regimen. While most people starting basal insulin continued sulfonylureas (70.9%), 38.9% or less continued sulfonylureas with other regimens (Table). Between 60% and 80% of those using thiazolidinediones discontinued on any regimen. Overall, people in south Asia and north Africa were more likely to continue sulfonylureas (55% and 56%) than those in China (7%); people in China were also more likely to discontinue metformin. In summary, while most people discontinued sulfonylureas and thiazolidinediones when starting any insulin with a mealtime component, marked variations in practice are found globally.

Table. Use of oral-glucose lowering drugs (OGLDs) before and after starting insulin therapy

	Premix	Basal	Mealtime only	Mealtime+ any basal	All
OGLDs alone prestudy (n)	22 532	10 351	2167	895	36 810
1 OGLD (%)	23.7	17.3	29.2	17.8	22.3
2 OGLDs (%)	55.9	56.5	56.6	49.4	55.7
>2 OGLDs (%)	20.3	26.2	14.2	32.8	22.1
Prestudy (% of insulin starters)					
Metformin	81.6	83.3	80.7	79.9	81.8
Sulfonylurea	73.3	83.4	64.7	82.0	75.7
Thiazolidinediones	18.9	22.3	16.1	23.7	19.9
α–glucosidase inhibitor	10.3	9.4	10.6	11.5	10.3
Continuing OGLD (% of prestudy OGLDs)					
Metformin	69.1	83.4	67.8	49.7	72.3
Sulfonylurea	38.9	70.9	37.1	18.8	47.8
Thiazolidinediones	21.6	40.5	23.3	17.5	27.3

Glinides, DPP4 inhibitors and others were below 10.0% in all groups

2316-PO

Patient Reported Outcomes Using Twice-Daily Insulin Aspart Premixed vs Insulin Glargine Plus 1 Prandial Insulin Glulisine or Stepwise Addition of Glulisine to Glargine in Type 2 Diabetes Uncontrolled with Oral Agents

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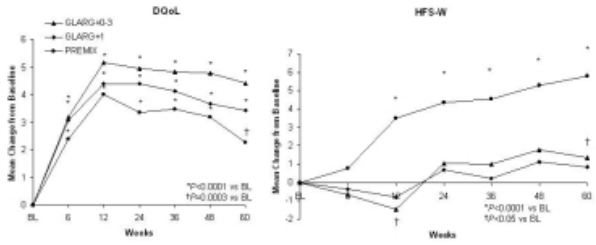
A 60-wk randomized, open-label study compared adding BID premixed 70/30 insulin aspart (PREMIX), basal insulin glargine + 1 prandial insulin glulisine dose (GLARG+1), or stepwise addition of prandial glulisine (GLARG+0-3) in 586 patients with uncontrolled type 2 diabetes on oral agents. Mean baseline parameters: A1C 9.4%; age 54y, diabetes duration 9y, BMI 33.2kg/m^2. While achieving similar glycemic control and body weight changes, GLARG+1 and GLARG+0-3 were more effective than PREMIX in FBG reduction and reaching A1C <7%, while causing less overall hypoglycemia. In the current analyses, patient reported outcomes were measured at baseline, 6, 12, 24, 36, 48, and 60 wks to assess overall quality of life (EQ-5D), diabetes-specific quality of life (DQoL), hypoglycemic fear (HFS-W), and adjustment to illness (Psychosocial Adjustment to Illness Scale-Self Report: PAIS-SR) (GLARG+1:n=195, GLARG+0-3:n=194, PREMIX:n=197). No significant between-group differences observed for EQ-5D and only at wk 60 for GLARG+0-3 vs PREMIX for PAIS-SR, but DQoL and HFS-W for GLARG+1 and GLARG+0-3 improved vs PREMIX. Time course of DQoL (+Δ=improved DQoL) and HFS-W (+Δ=more worry) shown in Fig. DQoL improved significantly for all groups at all wks; average improvement was greater for GLARG+1 and GLARG+0-3 vs PREMIX ($P \leq 0.0002$). Patients treated with PREMIX showed significantly greater hypoglycemic fear from wk 12 to study end ($P<0.05$). The three insulin regimens did not differentially influence overall QoL or adjustment to disease; however, glargine-based regimens led to greater improvement in DQoL vs PREMIX while avoiding increase in hypoglycemic fear, proving to be valid therapeutic regimens.



Supported by: sanofi-aventis US

2317-PO

Pharmacokinetic/Pharmacodynamic Modeling of TAK-875, a Novel GPR40 Agonist, in Japanese Patients with Type 2 Diabetics

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TAK-875 is a highly selective GPR40 agonist which potentiates glucose-stimulated insulin secretion, and is expected to be a new oral antidiabetic drug with a low risk of inducing hypoglycemia in clinical use. The objective of this exploratory analysis was to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TAK-875 in subjects with type 2 diabetes mellitus (T2DM) and to support the design of subsequent studies using a population model-based analysis approach.

An early phase 2, randomized, placebo-controlled, double-blind, parallel-group study was performed with 3 arms of TAK-875 (100 or 400 mg) or placebo once daily for 14 days in Japanese T2DM patients with insufficiently controlled blood glucose despite diet or exercise. A total of 44 subjects receiving TAK-875 (100 mg n=22; 400 mg n=22) were included in the population PK analysis. Sequential PK/PD analysis using an indirect response model was performed on all data including the placebo group (n=21). This was applied to describe the relationship between TAK-875 plasma concentrations and fasting plasma glucose (FPG) using a non-linear mixed effect modeling approach.

TAK-875 plasma concentrations were adequately described by a 1-compartment model with first-order absorption and elimination. Two covariates were selected in the final model: Weight on oral clearance, BMI on distribution volume. Comparing TAK-875 exposure of T2DM and healthy subjects, mean Cmax values from T2DM subjects were comparable to that observed from healthy subjects, whilst AUC in T2DM was about 1.6 fold higher than those in healthy subjects.

The indirect response model for FPG was applied without taking account of disease progression since the study consisted of a 2-week treatment and 1-week follow-up period, in addition observed FPG changes in placebo group were almost zero. The developed PK/PD model was then used to simulate the expected changes in FPG in a Phase 2b dose ranging trial. The application of PK/PD modeling quantified the relationship between PK and FPG and allowed for the design of subsequent studies to be evaluated, thus being a useful tool to support the clinical development program.

2318-PO

Pharmacokinetics and Pharmacodynamics of BI 10773, a Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor, and Linagliptin, a Dipeptidyl Peptidase-4 (DPP-4) Inhibitor, Following Co-Administration in Healthy Volunteers

CHRISTIAN FRIEDRICH, KATRIN METZMANN, PETER ROSE, MICHAELA MATTHEUS, SABINE PINNETTI, HANS J. WOERLE, *Biberach an der Riss, Germany, Ingelheim am Rhein, Germany*

This open-label study investigated potential drug-drug interactions between the SGLT-2 inhibitor BI 10773 and the DPP-4 inhibitor linagliptin. Sixteen healthy males received treatment A (50 mg qd BI 10773 for 5 days), B (50 mg qd BI 10773 and 5 mg qd linagliptin for 7 days) and C (5 mg qd linagliptin for 7 days) in treatment sequence A+B then C or C then A+B. The washout period between B and C or C and A was at least 35 days. Co-administration

For author disclosure information, see page 785.

of linagliptin had no effect on the extent of BI 10773 absorption ($AUC_{\tau,ss}$ geometric mean ratio [GMR] 101.7%; 90% CI 96.5%, 107.2%). There was a slight, clinically non-significant reduction in the rate of absorption ($C_{max,ss}$ GMR 88.3%; 90% CI 78.8%, 98.9) of BI 10773. Co-administration of BI 10773 had no effect on the extent ($AUC_{\tau,ss}$ GMR 103.3%; 90% CI 96.1%, 111.1%) or rate ($C_{max,ss}$ GMR 101.5%; 90% CI 86.9%, 118.5%) of linagliptin absorption. BI 10773 alone and in combination with linagliptin led to a clinical relevant excretion of glucose in urine. DPP-4 inhibition was similar following linagliptin administration with BI 10773 or alone. Both BI 10773 and linagliptin were well tolerated. These data support co-administration of BI 10773 and linagliptin in clinical trials without dose adjustments.

Supported by: Boehringer Ingelheim Pharmaceuticals, Inc.

2319-PO

Pioglitazone Compared to Glibenclamide on Lipid Profile and Inflammation Markers in Type 2 Diabetic Patients during Oral Fat Load

GIUSEPPE DEROSA, ANGELA D'ANGELO, ILARIA PALUMBO, SABRINA RANDAZZO, LUCIO BIANCHI, PAMELA MAFFIOLI, *Pavia, Italy*

The aim of this study was to evaluate the effect of pioglitazone and glibenclamide on lipid profile and inflammatory parameters in 194 type 2 diabetic patients in treatment with metformin during a standardized oral fat load (OFL). Pioglitazone was titrated till 45 mg/day and glibenclamide till 15 mg/day, in association with metformin, respectively. Type 2 diabetic patients underwent an OFL at baseline, and after 12 months of this treatment. The OFL was given between 08.00 and 09.00 h after a 12-h fast. Blood samples was drawn before and 3, 6, 9, and 12 h after the OFL. We evaluated total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), interleukin-6 (IL-6), high sensitivity C-reactive protein (Hs-CRP), and tumor necrosis factor-α (TNF-α). At 12 months OFL, TC and LDL-C were significantly reduced at 6 and 9 hours in pioglitazone group compared to glibenclamide (13±5 vs 5±2 mg/dl; 8±3 vs 4±1 mg/dl, $p< 0.05$, respectively); HDL-C was significantly changed at 6 hour in pioglitazone group compared to glibenclamide group (7±3 vs -2±1 mg/dl, $p< 0.05$), and Tg was significantly reduced at 6 and 9 hours in pioglitazone group compared to glibenclamide group (63±14 vs 23±8 mg/dl; 49±11 vs 28±9 mg/dl, $p< 0.01$, and $p< 0.05$, respectively). A significant IL-6 reduction was obtained at 3, and 6 hour in pioglitazone group compared to glibenclamide group (0.5±0.1 vs 0.3±0.05 pg/ml; 0.9±0.4 vs 0.1±0.008 pg/ml, $p< 0.05$, and $p< 0.01$, respectively). A significant Hs-CRP reduction was observed at 6 and 9 hour in pioglitazone group compared to glibenclamide group (1.1±0.08 vs 0.4±0.005 mg/l; 0.9±0.05 vs 0.2±0.001 mg/l, $p< 0.01$, and $p< 0.05$, respectively), and a significant TNF-α reduction was seen at 6 hour in pioglitazone group compared to glibenclamide group (0.9±0.1 vs 0.3±0.05 ng/ml, $p< 0.05$). Seven patients reported some side effects during OFL and three patients interrupted the test. In conclusion, pioglitazone treatment mitigated the variations of lipid components and inflammation parameters compared to glibenclamide treatment.

2320-PO

Pooled Analysis Reveals Greater Glycemic Control with Insulin Glargine vs Comparators in Adults Aged 65-74 and ≥75 Years

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Achieving adequate glycemic control may be difficult in the elderly due to many medical factors and functional impairment. A pooled analysis of 24-week data from 9 randomized controlled trials evaluated safety and efficacy differences in patients aged 65-74 (n=311 younger IG [YIG]; n=304 younger C [YC]) or ≥75 years (n=25 older IG [OIG]; n=35 older C [OC]) receiving insulin glargine (IG) vs comparators (C) (OADs, insulin [NPH, lispro, premixed] and diet) and also compared young vs old within each treatment group. Within the IG and C groups, young and old patients had similar changes in A1C, fasting plasma glucose (FPG), weight, BMI, and insulin dose (both IU and IU/kg) and were just as likely to reach A1C<7.0%. Compared with YC, YIG patients were significantly more likely to achieve A1C<7.0%, (P=0.006), had greater reductions in A1C (P=0.014) and FPG (P<0.001), and a smaller increase in insulin dose (P<0.001). Among older patients, OIG had a significantly lower increase in insulin dose (IU/kg) (P=0.047) and showed a trend (P=0.055) toward greater reduction in FPG vs OC. No differences in hypoglycemia (hypo) incidence or event rates in YIG vs OIG or YC vs OC emerged. Incidence and event rates of daytime and any hypo (self-monitored blood glucose [SMBG] <50 and <70 mg/dl) were significantly lower for YIG vs YC. The incidence rate of any hypo (SMBG <70 mg/dl) and event rates of any (SMBG <50 and <70 mg/dl) and daytime (SMBG <50 mg/dl) hypo were significantly lower for OIG vs OC. In conclusion, YIG patients had better glycemic control vs YC patients, with smaller increase in insulin dose and reduced any and daytime hypo risk. Although the sample of patients ≥75 years was small, the trend in better FPG and hypo outcomes with IG warrants further study.

Table. Treatment Outcomes at 24 Weeks: YIG vs YC and OIG vs OC

Variable	IG	C	*P* Value (IG vs C)
Age 65-74 Years			
A1C <7.0% at endpoint, % patients[a]	57.2	47.4	0.006
Adjusted ΔA1C, %[b]	−1.59	−1.44	0.014
Adjusted ΔFPG, mg/dl[b]	−74.30	−52.08	<0.001
Adjusted Δweight, kg[b]	1.53	1.53	0.993
Adjusted Δinsulin dose, IU[b]	18.08	30.27[c]	<0.001
Total hypoglycemia, SMBG <50 mg/dl, % patients	20.00	37.07	<0.001
Daytime hypoglycemia, SMBG <50 mg/dl, % patients	16.33	32.31	<0.001
Nocturnal hypoglycemia, SMBG <50 mg/dl, % patients	6.00	9.52	0.156
Age ≥75 Years			
A1C <7.0% at endpoint, % patients[a]	48.0	45.7	0.843
Adjusted ΔA1C, %[b]	−1.47	−1.32	0.456
Adjusted ΔFPG, mg/dl[b]	−70.70	−50.50	0.055
Adjusted ΔBMI, kg/m²[b]	0.22	0.39	0.580
Adjusted Δinsulin dose, IU[b]	17.29	26.14[c]	0.227
Total hypoglycemia, SMBG <50 mg/dl, % patients	4.00	23.53	0.058
Daytime hypoglycemia, SMBG <50 mg/dl, % patients	4.00	23.53	0.058
Nocturnal hypoglycemia, SMBG <50 mg/dl, % patients	0.00	2.94	0.414

[a]Unadjusted data. [b]Adjusted for baseline.
[c]C includes NPH insulin, insulin lispro, and premixed insulin only.

Supported by: sanofi-aventis, US

2321-PO

Predictors of the Composite Endpoint (A1C <7%, Weight Change ≤0 kg and No Hypoglycemia) at 6 Months Following the Initiation of Biphasic Insulin Aspart 30 (BIAsp 30) in Patients with Type 2 Diabetes (T2D) on Prior Oral Antidiabetic Drug Therapy

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IMPROVE was a multinational, 26-week observational study evaluating BIAsp 30 use in routine clinical practice. Logistic regression analysis was used to identify predictors for the composite endpoint (A1C <7%, weight change ≤0 kg and no hypoglycemia) in insulin-naive patients (n=23,483) from the IMPROVE study, who initiated BIAsp 30. Results from multivariate analysis (including sex, diabetes duration, age, baseline A1C, baseline body mass index (BMI), hypoglycemia prior to insulin initiation and total insulin dose) are reported. Shorter duration of diabetes (p<0.0001), lower total daily insulin use (p=0.0042), male sex (p<0.0001), lower baseline A1C (p<0.0001), higher baseline BMI (p<0.0001), and no prior hypoglycemia (p<0.0001) were significant predictors for achieving A1C <7%, weight change ≤0 kg and no hypoglycemia (Table). These data support the early initiation of BIAsp 30 in patients with T2D in order to maximize the proportion achieving A1C targets without weight gain or hypoglycemia.

Table

	A1C <7%, weight change ≤0 kg, no hypoglycemia[1] Multivariate logistic regression[2]	
Value	**Odds ratio[3]**	***p*-value[4]**
Age (y)		
≤45	1.00	
>45–≤55	1.07	0.0819
>55–≤65	1.03	
>65	1.13	
Gender		
Female	1.00	<0.0001
Male	1.27	
Diabetes duration (y)		
≤5.0	1.00	<0.0001
>5.0–≤10.0	0.77	
>10.0–≤20.0	0.66	
>20.0	0.51	
BMI (kg/m^2)		
≤25.0	1.00	<0.0001
>25.0–≤27.5	1.47	
>27.5–≤32.5	1.56	
>32.5	1.29	
Any hypos at baseline[5]		
≥1	1.00	<0.0001
No hypos	1.46	
A1C (%)		
≤7.4	1.00	
>7.4–≤8.2	0.67	<0.0001
>8.2–≤9.2	0.48	
>9.2	0.36	
Total daily insulin dose (IU/kg)		
≤0.15	1.00	0.0042
>0.15–≤0.20	0.79	
>0.20–≤0.30	0.76	
>0.30	0.81	

1. Data from the efficacy analysis set
2. Logistic regression models the probability of the event response on all
3. Value 1.00=reference level. Lower value=lower probability
4. *p*-value for testing the variable in logistic regression with all variables included in the model
5. Combined major (0–13 weeks) and minor hypoglycemia (0–4 weeks) before baseline

Supported by: Novo Nordisk A/S

2322-PO

Randomized Double-Blind Clinical Trial Comparaing Efficacy and Safety of Pioglitazone and Metformin in Patients with Type 2 Diabetes

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The present study was undertaken to asseses the efficacy and safety of two different insulin sensitizers- Pioglitazone (PIO) and Metformin (MET) in Bangladeshi T2DM subjects. This was a prospective, randomized, double-blind, cross-over study. Seventy seven T2DM patients with (HbA1c £ level 7.1%) were randomized to receive treatment (PIO 30 mg/day or MET 850 mg/day) for 3 months followed by a 2- week "metformin wash-out period", then crossed over to the alternative treatment regimen for a further 3 months. Outcome measures included BMI, HbA1c, fasting and 2 hours blood glucose (FBG and 2hBG respectively), insulin levels, total cholesterol (TC), high and low density lipoprotein cholesterol (HDL-C and LDL-C respectively), triglyceroides, SGPT and creatinine. Sixty one patients [24 men and 37 Women, aged 46±0.6yrs, BMI 26±0.4 (M±SEM)] completed the study. BMI increased significantly (p=0001) in PIO group and decreased nonsignificantly in MET group compared to baseline. Mean HbA1c decreased by 0.14% and 0.01% in patients receiving PIO and MET respectively. After treatment with PIO, FBG and 2hBG decreased significantly (p=0.002 and p=0.0001 respectively) from baseline whereas no improvement was found in FBG and 2hBG with MET treatment. Significant reduction in LDL-C (P=0.022) and non significant reduction in TC (p=0.09) was found with MET. After 3 months treatment PIO enhanced HOMA%S with baseline [42.0(16.2-227.2) vs 62.5(15.2-197.4);p=0.081]. Similarly PIO increased QUICKI [baseline vs end point 0.53±0.01 vs 0.57±0.01; p=0.007] and decreased HOMA-IR (4.7±3.5 vs 3.2±2.2; p=0.002). MET showed no significant effect on HOMA%B, HOMA%S or HOMA-IR. Both the treatments decreased serum SGPT and increased serum creatinine significantly. Both the therapy were equally tolerated and the overall frequency of adverse events was similar between treatment groups although their adverse events profile differed. In conclusion, pioglitazone was superior to metformin for the improvement of glycemic control and markers associated with increased insulin resistance in Bangladeshi T2DM subjects.

2323-PO

Real World Clinical Experience with Exenatide, a Long Term Study on Weight and A1c Control

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We evaluated the sustained efficacy of exenatide added to oral anti-diabetic therapy in patients who were either insulin naïve (group A, n=50) or insulin requiring (group B, n=47). A single physician in a private practice endocrinology office made the clinical decision to add exenatide as needed to improve A1c to a target less than 6.5%. Baseline therapies were composed of combinations of metformin, pioglitazone, sulfonylurea and insulin. All patients were titrated from 5 to 10mcg SQ of exenatide BID as tolerated and all sulfonylureas were discontinued. In group A, exenatide was the only injectable agent used during the follow-up period. Measurements of weight, weight, A1C, blood pressure, lipids, and insulin utilization were assessed every 3 months for a maximum of 48 months after initiation of exenatide. Group A patients had a mean duration of diabetes of 7.9±0.7 yr (±SD) and a mean A1c of 7.1±1.9%. Group B patients had a mean duration of diabetes of 15.4±0.9 yr and a mean A1c of 8.1±0.6%. Mean A1C at 48 months for Group A (fig.1) was 6.04% ±0.8 (p= 0.0001), and 6.94% ±0.6 (p= 0.0011) for Group B (fig.2). Mean weight change was −6.8 kg ±9.8 (p = <0.0001) for Group A (fig.1) and -7.3 kg ±8.1 (p = <0.0001) for Group B (fig.2). The addition of exenatide to combination oral therapy results in sustained weight loss, BP reduction, improved A1C and non-HDL values for both groups with substantial reductions in the total daily dose of insulin for Group B.

fig 1: Group A (non-insulin users)

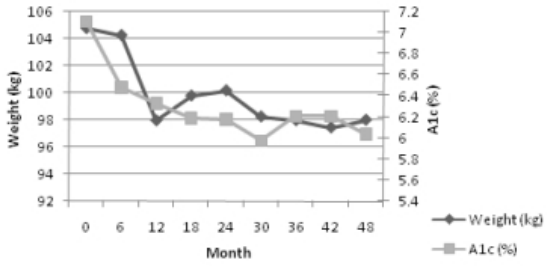
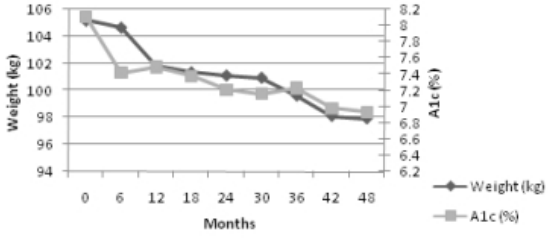


fig 2: Group B (insulin users)



2324-PO

WITHDRAWN

For author disclosure information, see page 785.

2325-PO

Replacement of NPH Insulin with Insulin Glargine Provided Significantly Better Glycemic Control in Patients with Type 2 Diabetes Uncontrolled on NPH Plus Oral Antihyperglycemic Drugs or Short-Acting Insulin

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An observational study was undertaken in Russia to monitor the efficacy and safety of insulin glargine in patients with type 2 diabetes mellitus (T2DM) whose hyperglycemia was uncontrolled on NPH insulin in combination with oral antihyperglycemic drugs (OADs) or short-acting insulins. Eligible patients were those starting treatment with glargine plus OADs or short-acting insulin after failing to achieve glycemic control with NPH insulin plus OADs or short-acting insulin. Patients continued their OAD or short-acting insulin treatment. The primary end point was change in mean A1C following 24 weeks of glargine treatment. Secondary end points included change in fasting blood glucose (FBG) and daily dose of glargine and hypoglycemic episodes. Data for 7334 enrolled patients were included in the analyses; 6802 patients were evaluated for efficacy. Patients had a mean age of 58.3 ± 9.0 years and a mean duration of T2DM of 10.5 ± 4.7 years; 68.1% were females. Mean A1C was 9.6 ± 1.7% at baseline and 7.2 ± 1.0% at 24 weeks. Change in mean A1C at 24 weeks was -2.4 ± 1.5% ($P < 0.001$). Mean FBG at baseline was 10.3 ± 2.5 mmol/l; the change at 24 weeks was -4.1 ± 2.3 mmol/l ($P < 0.001$). Mean daily dose of glargine was 19.4 ± 8.8 IU at baseline and 29.0 ± 10.2 IU at 24 weeks ($P < 0.001$). The dose of short-acting insulin did not change. In the 3 months prior to baseline, 17.3% of patients had experienced ≥ 4 mild hypoglycemic episodes. At 24 weeks, 2.2% of patients had experienced ≥ 4 mild hypoglycemic episodes ($P < 0.001$). Severe hypoglycemic episodes had been experienced by 3.1% of patients prior to baseline, and by 0.1% at 24 weeks ($P < 0.001$). There were 3 nonserious adverse events (AEs), of which 2 were mild and moderate hypoglycemic episodes, and 1 serious AE (acute stroke). For patients with T2DM uncontrolled by NPH insulin in combination with OADs or short-acting insulin, replacement of NPH insulin with glargine provided significantly improved glycemic control with fewer episodes of hypoglycemia.

Supported by: sanofi-aventis

2326-PO

Safety and Efficacy of Long Acting Glucagon like Peptide-1 Agonists Compared to Other Incretin-Based Therapies in Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Long acting glucagon like peptide-1 receptor agonists (LA-GLP-1RA) may deliver additional therapeutic benefits over other available incretin-based therapies (IBTs). The objective of this systematic review and meta-analysis was to pool results of English language, randomized, controlled trials of at least 24 weeks in duration comparing the safety and efficacy of maximum dose LA-GLP-1RA (liraglutide, exenatide once weekly, albiglutide, lixisenatide) to other available IBTs (exenatide, sitagliptin, saxagliptin) in patients with type 2 diabetes. We searched PubMed, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, EMBASE (inception-December 2010), and abstracts presented at the American Diabetes Association Scientific Sessions in 2009 and 2010 to identify studies. The primary endpoint was mean change in hemoglobin A1c (HbA1c) from baseline to study endpoint. Weighted mean differences or odds-ratios (ORs) and their 95% confidence intervals for each outcome relative to control were calculated as appropriate. HbA1c was reduced favoring LA-GLP-1RA (-0.52%;-0.66% to -0.39%). LA-GLP-1RA therapy was associated with an OR of 2.72 (1.81-4.09) for reaching the HbA1c target goal of <7%. Fasting plasma glucose (FPG) was reduced and favored the LA-GLP-1RA based regimens (-1.10 mmol/L;-1.40 mmol/L to -0.86 mmol/L). Exenatide twice daily demonstrated significantly greater reductions in post-prandial glucose (PPG) after the morning and evening meals compared to LA-GLP-1RA. Body weight was reduced similarly between LA-GLP-1RA and exenatide, but favored LA-GLP-1RA in the sitagliptin comparator trials (-1.99 kg;-2.69 kg to -1.09 kg). LA-GLP-1RA therapy was not associated with severe hypoglycemia or acute pancreatitis. Nausea, vomiting, and diarrhea with LA-GLP-1RA were only increased relative to sitagliptin therapy with ORs of 4.70 (1.81-12.24), 3.22 (1.63-6.36), and 2.32 (1.42 to 3.81), respectively. Compared to other IBTs, LA-GLP-1RA produce greater improvement in HbA1c and FPG, lesser effect on PPG, similar reduction in body weight, and result in a comparable adverse event profile.

2327-PO

Safety and Tolerability of Linagliptin: A Pooled Analysis of Data from 3572 Patients with Type 2 Diabetes

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Achieving long-term glycemic control in type 2 diabetes mellitus (T2DM) requires treatments that are effective but also well tolerated. Dipeptidyl peptidase (DPP)-4 inhibitors provide clinically meaningful efficacy and are well tolerated. The most commonly observed adverse events (AEs) listed in labels of currently available DPP-4 inhibitors include infections, headache, and hypersensitivity; other AEs of interest include renal or hepatic dysfunction and hypoglycemia.

To extend current knowledge of the safety and tolerability profile of linagliptin, a new DPP-4 inhibitor currently in late-stage development, a large pooled-analysis of 3572 patients with T2DM was conducted. Data from 8 randomized, placebo-controlled, Phase 3 clinical trials were analyzed. 2523 and 1049 patients received linagliptin 5 mg qd or placebo, respectively.

The overall incidence rate of AEs or serious AEs with linagliptin was similar to placebo (AEs 55.0% vs 55.8%; serious AEs 2.8% vs 2.7%). Overall aggregated infection rates were 19.5% for linagliptin and 21.4% for placebo. Fewer or similar rates of AEs vs placebo were seen with linagliptin for upper respiratory tract infection (3.3% vs 4.9%), headache (2.9% vs 3.1%), urinary tract infection (2.2% vs 2.7%), blood and lymphatic disorders (1.0% vs 1.2%), hypersensitivity (0.1% vs 0.1%), hepatic enzyme increase (0.1% and 0.1%), and serum creatinine increase (0.0% and 0.1%). There was a slight increased frequency of nasopharyngitis (5.9% vs 5.1%) and cough (1.7% vs 1.0%) with linagliptin. In general, hypoglycemia rates were similar with linagliptin (8.2%) and placebo (5.1%). Incidence of hypoglycemia was increased in patients with background sulfonylurea (SU) therapy (linagliptin 20.7%), which is in agreement with other reports where DPP-4 inhibitors were added to SUs. Overall, the hypoglycemic event rate with linagliptin was very low (<1.0%) when used without SUs.

This large pooled analysis provides further evidence that linagliptin is well tolerated. Continued assessment of AEs reported from the ongoing clinical trial program is desirable to establish its long-term safety.

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2328-PO

Safety Profile of Saxagliptin (SAXA) in Combination with 2 Other Agents: Data from Dual-Therapy Trials in Patients Receiving Rescue Treatment

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SAXA, a selective DPP-4 inhibitor, has been studied as initial combination with metformin (MET) and as add-on therapy to MET, sulfonylurea (SU), or thiazolidinedione (TZD) in patients (pts) with inadequately controlled type 2 diabetes in 4 randomized, double-blind trials of 24-wk short-term duration with either a blinded 42-mo (MET add-on trial) or 52-wk long-term extension period (Table). Those not achieving glycemic control per study criteria received study-dependent rescue medication. This descriptive post hoc analysis describes the safety experience of SAXA in a cohort of pts concurrently treated with 2 other oral agents (including 1 added as rescue). There were no deaths; 5 treatment-related serious adverse events (SAEs) occurred. Overall, AE rates (Table) were comparable for differing combinations of SAXA with MET plus either SU or TZD. Most common AEs were similar to those described in the overall SAXA clinical trials program. Among 624 pts who took SAXA 2.5, 5, or 10 mg combined with MET and TZD therapy, 20 had hypoglycemic events (incidence, 0.7–5.0%) and 3 had confirmed events (glucose ≤50 mg/dL; incidence, 0–0.8%). In pts with combined SAXA, MET, and SU therapy (n=305), 14.8% had hypoglycemic events and 3.3% had confirmed hypoglycemia. In conclusion, this post hoc analysis of add-on therapy trials demonstrated that SAXA combined with MET and TZD or MET and SU as part of rescue therapy was well tolerated with infrequent episodes of confirmed hypoglycemia and a low proportion of pts having any hypoglycemic event.

Combination of SAXA *plus*	Rescue	SAXA dose	Received rescue, n	Mean (SD) duration of rescue, wk	≥1 AE, %	≥1 SAE, %	D/C due to AE, %
TZD (pioglitazone 30 or 45 mg or rosiglitazone 4 or 8 mg)	MET	2.5 mg (n=195)	65	31 (15)	49	5	3
		5 mg (n=186)	45	36 (15)	51	4	0
MET 1500–2500 mg	Pioglitazone	2.5 mg (n=192)	132	79 (43)	68	8	3
		5 mg (n=191)	113	78 (48)	69	11	6
		10 mg (n=181)	118	78 (46)	74	8	3
MET titrated to 1000-2000 mg	Pioglitazone	5 mg (n=320)	70	25 (16)	41	3	1
		10 mg (n=323)	81	24 (15)	31	1	0
Glyburide 7.5 mg vs uptitration to ≤15 mg	MET	2.5 mg (n=248)	149	32 (16)	57	2	5
		5 mg (n=253)	156	34 (15)	60	1	3

2329-PO

Saxagliptin in Combination with Metformin Allows More Patients To Reach a Composite End Point of HbA_{1c} <7% without Weight Gain or Hypoglycemia

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Outcome trial data suggest that hypoglycemia is a risk factor for mortality. Weight loss is a centerpiece of diabetes care. The fact that many diabetes therapies increase risk for hypoglycemia and weight gain is problematic. Saxagliptin (SAXA), a potent DPP-4 inhibitor, effectively lowers HbA_{1c} with low incidence of hypoglycemia and is weight neutral. Because metformin (MET) is a common first-line therapy in type 2 diabetes and a fixed-dose combination of SAXA+MET has recently been approved, a post hoc analysis of 2 phase 3 clinical studies of SAXA+MET was performed to compare the proportion of patients (pts) achieving a composite end point at 24 wk (last observation carried forward [LOCF]) of HbA_{1c} <7% + no weight gain (<2% body wt increase) + no reported hypoglycemia in pts receiving SAXA 5 mg as add-on to or initial combination with MET. In the add-on study, pts inadequately controlled by MET alone (baseline HbA_{1c} 7–10%) were randomized to receive SAXA+MET or placebo (PBO)+MET. In the initial combination study, treatment-naïve pts (baseline HbA_{1c} 8–12%) were randomized to SAXA+MET or PBO+MET. In both studies, the combination of SAXA+MET improved glycemic control as measured by changes in HbA_{1c} and fasting and postprandial plasma glucose. In the add-on study, more pts on SAXA+MET (39.8%) achieved the composite end point vs pts on PBO+MET (11.4%; Table). Likewise, in the initial combination study, more pts treated with SAXA+MET (52.1%) achieved the composite end point vs pts on PBO+MET (34.1%; Table). In summary, the combination of SAXA+MET produced a higher proportion of pts achieving glycemic control without weight gain or hypoglycemia.

	Add-on to MET		Initial Combination Study	
End point at wk 24 (LOCF)	**SAXA 5 mg + MET (n=186)**	**PBO+MET (n=175)**	**SAXA 5 mg + MET (n=307)**	**PBO+MET (n=314)**
HbA_{1c} <7%, n (%)	81 (43.5)	29 (16.6)	185 (60.3)	129 (41.1)
No hypoglycemia, n (%)	176 (94.6)	166 (94.9)	296 (96.4)	301 (95.9)
Weight gain <2%, n (%)	163 (87.6)	157 (89.7)	270 (87.9)	280 (89.2)
Composite end point reached, n (%)	74 (39.8)	20 (11.4)	160 (52.1)	107 (34.1)
Difference vs control, % (95% CI)	28.4 (19.7–36.8)		18.0 (10.2–25.7)	

2330-PO

WITHDRAWN

2331-PO

Short- and Long-Term Effects of Pitavastatin and Simvastatin on Serum Uric Acid Levels in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia and ≥2 Risk Factors for Coronary Heart Disease

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Elevated levels of serum uric acid (SUA) may increase the risk of coronary heart disease (CHD) events, independently of traditional CHD risk factors. Lipid modifying agents have been shown to reduce SUA; however, limited information is available on this effect with pitavastatin (PTA). Therefore, this *post hoc* analysis assessed the short- and long-term effects of PTA on changes in SUA over a 12- to 56-week period compared with simvastatin (SIM) in patients with primary hyperlipidemia (PH) or mixed dyslipidemia (MD) and ≥2 risk factors for CHD. SUA data were prospectively collected as part of a 12-week, randomized, double-blind, multinational phase 3 study comparing PTA 4 mg (n=233) with SIM 40 mg (n=118) in patients with PH or MD and ≥2risk factors for CHD (NK-104-304). Treatment groups were well matched in terms of demographic and risk factors for CHD including arterial hypertension. After 12 weeks, 173 patients were enrolled in the extension study [PTA 4 mg (N=121) and SIM (N=52)] and followed for an additional 44 weeks (NK-104-309). Changes in SUA levels from baseline to end of the 12-week trial and through completion of the extension period (56 weeks total) were assessed using Student's paired t-tests. PTA significantly decreased SUA levels (mean changes in mg/dL±SD) in patients with PH or MD and ≥2 risk factors for CHD at both 12 weeks (PTA: -0.15±0.75, p=0.002 vs. SIM: -0.07±0.72, p=0.342) and 56 weeks (PTA: -0.17±0.69, p=0.008 vs. SIM: -0.25±0.60, p=0.005). After excluding patients with diabetes and those on diuretics, consistent results were observed for PTA (n=178, -0.11±0.71, p=0.038 at 12 weeks and n=89, -0.17±0.64, p=0.016 at 56 weeks) and SIM (n=85, 0.02±0.73, p=0.83 at 12 weeks and n=35, -0.17±0.57, p=0.094 at 56 weeks). Both short (12-week) and long-term (56-week) therapy with PTA significantly decreased SUA in patients with PH or MD and ≥2 risk factors for CHD.

Supported by: KPA, Inc. and Lilly USA, LLC

2332-PO

Sitagliptin (SITA) Provides Similar Glycemic Control with Weight Loss and Less Hypoglycemia Compared to Sulfonylurea (SU) in Older Patients with Type 2 Diabetes (T2DM)

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With advancing age, patients (pts) with T2DM generally have more comorbidities and can present unique therapeutic challenges. SUs are commonly used agents for T2DM in pts who have inadequate glycemic control on metformin (MF). However, SUs increase the risk of hypoglycemia (HYPO), which often is more pronounced in older pts and can lead to more serious consequences including falls and fractures. DPP-4 inhibitors, such as SITA, improve glycemic control and are generally well tolerated with a low risk of HYPO when used alone or in combination with MF. The present post-hoc analysis compared the effects of the addition of SITA or SU on change from baseline (BL) in A1C and body weight (BW) and the incidence of symptomatic HYPO in a subgroup of pts ≥65 yrs from 2 randomized, double-blind studies conducted in pts with inadequate glycemic control on MF (≥1500 mg/d). In study 1, pts (BL A1C 6.5-10%) were randomized 1:1 to SITA 100 mg/d or glipizide (GLIP 5 mg/d, uptitrated to a potential 20 mg/d over the initial 18 wks) for 52 wks. In study 2, pts (BL A1C 6.5-9%) were randomized 1:1 to SITA 100 mg/d or glimepiride (GLIM 1 mg/d, uptitrated to a potential 6 mg/d over the initial 18 wks) for 30 wks. In each study from a BL A1C of ~7.5%, the decrease in A1C was similar and statistically significant with either treatment (Table). Both treatments were generally well tolerated; however, a significantly ($p<0.05$) lower incidence of HYPO was observed with SITA than with SU. BW decreased with SITA, but increased with SU. In these studies, the addition of SITA to pts ≥65 yrs with T2DM failing MF monotherapy provided similar A1C-lowering efficacy, with less HYPO and with BW loss rather than BW gain, compared to the addition of SU.

For author disclosure information, see page 785.

	Study 1- 52 weeks (N=243)		Study 2 - 30 weeks (N=217)	
	SITA	GLIP	SITA	GLIM
ΔA1C, %	-0.7 (-0.9, -0.5)	-0.7 (-0.8, -0.5)	-0.4 (-0.6, -0.3)	-0.5 (-0.7, -0.4)
ΔBW, kg	-1.4 (-2.6, -0.3)	1.1 (0.0, 2.1)*	-0.9 (-1.5, -0.2)	1.1 (0.5, 1.8)*
HYPO, % of pts	5.0	39.0*	7.6	17.9**

ΔA1C and ΔBW are least squares mean change from BL (95% CI)
*p<0.001 or **p<0.05 for difference between groups within study

2333-PO

Sitagliptin Compared to Thiazolidinediones as a Third-Line Oral Anti-Hyperglycemic Agent in Ethnic Minority Type 2 Diabetic Patients

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We compared sitagliptin versus thiazolidinediones (TZDs) when used as a third-line oral agent among poorly controlled, ethnic minority type 2 diabetic patients sub-optimally controlled on maximum-tolerated doses of metformin plus a sulfonylurea. One hundred and eight subjects were given sitagliptin 100 mg daily in an open-label fashion for up to 12 months, and results were compared to an historical control group of 104 similar patients treated according to an identical treatment algorithm with TZDs (rosiglitazone 8 mg or pioglitazone 45 mg daily) as their third-line oral agent. Compliance was determined by pill counts and dietary and lifestyle principles were reinforced at bi-monthly visits for 1 year. Outcomes included the change in HbA_{1c} from baseline to 4 months, the proportion of subjects achieving HbA_{1c} <7.5% (our threshold for starting insulin) at 4 months, and the proportion of these subjects maintaining their HbA_{1c} <7.5% by 12 months. Sitagliptin- and TZD-treated subjects were similar at baseline (HbA_{1c} 9.4 ± 1.8% vs. 9.4 ± 1.9% respectively; known diabetes duration 6.7 ± 5.0 years vs. 7.6 ± 5.8 years, respectively; p=NS). HbA_{1c} decreased in both groups at 4 months (p<0.001 for both groups), but the reduction was greater with TZDs than sitagliptin (-2.0 ± 1.7% vs. -1.3 ± 1.8%; p=0.006), as was the proportion of subjects achieving HbA_{1c} <7.5% (61.5% vs. 46.1%; p=0.026). Of all subjects achieving HbA_{1c} <7.5% at 4 months, similar proportions in each group sustained their HbA_{1c} <7.5% by 12 months (59.1% vs. 57.8%; p=NS). Of the 55 sitagliptin subjects who failed to maintain HbA_{1c} <7.5s% and were switched pioglitazone 45 mg daily, 27.3% achieved HbA_{1c} <7.5% after a mean of 4 months on pioglitazone. Sitagliptin was well tolerated and did not precipitate weight gain or significant hypoglycemia; compliance remained >95%. Among poorly controlled, ethnic minority type 2 diabetic patients on maximum tolerated doses of metformin and sulfonylureas, third-line therapy with TZDs was more effective than sitagliptin after 4 months.

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ADA-Funded Research

2334-PO

Successful Switch from Insulin Therapy to a Metformin/Saxagliptin Combination Therapy in Patients with Type 2 Diabetes. Interim Results from the SAXAswitch Study

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Patients with type 2 diabetes mellitus may suffer from different degrees of vascular and metabolic insulin resistance and β-cell dysfunction. We have previously shown that patients on insulin treatment can be successfully switched back to oral treatment with insulin sensitizers, if insulin resistance is the predominant disorder. In this study, we investigate whether patients with residual β-cell function (low proinsulin and normal C-peptide levels) can be switched back to a combination treatment with saxagliptin and metformin (Saxa+Met). Patients on insulin therapy for more than one year and a HbA1c <7.5% (n = 120) were subjected to a 1:2 randomization (21 women, 19 men, age: 63±8 yrs., disease duration: 10.8±5.0 yrs., BMI: 33.7±6.5 kg/m², HbA1c: 6.8±0.5 %) to stay on insulin or to switch to an oral combination therapy with 2x 850 mg of metformin and 5 mg saxagliptin (33 women, 47 men, 63±9 yrs., 11.7±7.6 yrs., BMI: 33.5±5.0 kg/m², HbA1c: 6.8±0.5 %). In case of worsening of glycemic control (HbA1c increase > 0.4 %), pioglitazone was provided as first rescue medication (+Pio), insulin glargine served as 2nd rescue drug (+Glarg). At the time point of this interim analysis, all 120 patients were at least 4 months in the study and 31 patients had already completed the six-month trial with stable glycemic control. Only 2/40 patients had dropped out in the insulin group (5.0 %, protocol violations, 13 completers) and 9/80 patients stopped the study prematurely in the oral treatment group (11.3 %, 18 completers). From the 18 completers on oral therapy, 10 were on Saxa+Met (55 %), 3 were on Saxa-Met-Pio (17 %), and 5 were on Saxa+Met+Pio+Glarg (28 %). There were no differences regarding type and severity of adverse events between the two treatment arms. In conclusion, combination of modern oral drugs may allow a successful switch back from insulin treatment to oral combination therapy in patients with residual β-cell function. Final analysis after completion of the entire trial may help to identify patient conditions or laboratory biomarkers with predictive value for such a successful switch.

Supported by: Astra Zeneca and BMS

2335-PO

Switching from an NPH Insulin to an Insulin Glargine Basal-Bolus Regimen Improves Glycemic Control in Diabetic Patients: The LINDA Study

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An observational study was undertaken in the Czech Republic to determine the safety and efficacy of insulin glargine (GLA) in patients with either type 1 (T1DM) or type 2 diabetes (T2DM). This was a multicenter, noninterventional, 24-week study in patients who had switched (for reasons unrelated to the study) from a predominantly NPH insulin basal-bolus regimen (87.2% of patients) to one with GLA. Prandial insulin was human insulin (65.2%) or an insulin analog (31.7%). Safety was assessed in all 4998 patients included in the study, while efficacy was assessed in 4819 patients who complied with protocol. The primary efficacy end point was change in A1C (IFCC methodology, target A1C = 5.4%). Secondary end points included percent of patients with A1C < 5.4% and change in fasting plasma glucose (FPG), body weight, and total daily insulin dose. Mean age of patients was 54 years; mean weight, 85.0 kg; mean BMI, 29.0 kg/m^2, and mean A1C, 8.0%. At 24 weeks, mean A1C decreased from 7.7 ± 1.7% to 6.4 ± 1.4% (P < 0.001) in T1DM patients and from 8.1 ± 1.6% to 6.7 ± 1.4% (P < 0.001) in T2DM patients. Target A1C < 5.4% was attained by 25.7% of T1DM patients and 17.3% of T2DM patients. FPG was reduced by 2.3 ± 2.5 mmol/l and 2.8 ± 3.1 mmol/l in T1DM and T2DM patients, respectively. Total daily insulin dose and body weight increased significantly in T1DM patients (both P < 0.001) whereas they declined significantly in T2DM patients (both P < 0.001). BMI was not significantly affected in either group. In the last 4 weeks with NPH, 42.5% of all patients experienced a hypoglycemic event (HE); serious HEs and serious nocturnal HEs were experienced by 17.4% and 13.8% of all patients, respectively. In the last 4 weeks with GLA, 17.6% of patients experienced an HE; only 0.8% and 0.3% of patients reported serious and serious nocturnal HEs. Serious HEs were reduced from 3.5 to 0.02 HEs/patient/year (P < 0.001). The results show that switching from a basal-bolus regimen with NPH insulin to one with insulin glargine improved glycemic control in patients with T1DM or T2DM, with a reduction in hypoglycemic events.

Supported by: sanofi-aventis

2336-PO

Systematic Review on Berberine in the Treatment of Type 2 Diabetes

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To assess the efficacy and safety of berberine (an isoquinoline alkaloid) in the treatment of type 2 diabetes we searched electronic databases including PubMed (1978~2010), Medline (1996~2010), Excerpta Medica Database (1974~2010), Cochrane library, Chinese Biomedical Literature Database (1978~2010), the Chinese Scientific and Technical Journals database (1989~2010) and Chinese National Knowledge Infrastructure databases (1994~2010) and selected randomized clinical trials (RCTs) of berberine in the treatment of type 2 diabetes. Two authors of us independently extracted datas and assessed the trials quality.Meta-analysis was conducted with RevMan 5.0 software. The meta-analysis of 10 included randomized clinical trials (RCTs),included 621 patients ,showed :There were significantly differences between berberine combined metformin or combined glipizide groups and metformin or glipizide groups in the total efficacy of lowering blood glucose and/or reguleting blood lipids (P<0.05); There were significantly differences between berberine groups and metformin, glipizide or placebo groups in lowering HbA1c ,TG and TC (P<0.05) ;While there were no differences between the berberine groups and metformin, glipizide or palcebo groups in decreasing FBG and 2hPBG (P>0.05); There were no differences between the berberine groups and metformin, glipizide or palcebo groups in decreasing LDL-C and increasing HDL-C (P>0.05). Results suggest that berberine combined metformin or combined glipizide had a better effect than metformin or glipizide in the treatment of type 2 diabetes and berberine may decrease the leves of TG and TC. Berberine is effect and safe in treatment of type 2 diabetes.Due to the number and quality of included clinical trials and the number of patients were insufficent, the results should be confirmed by multi-centre,large, randomized double-blind control trials.

2337-PO

WITHDRAWN

2338-PO

The Development and Testing of a Novel Insulin-Eluting Stent

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Diabetes mellitus is known to increase the risk of restenosis after percutaneous intervention, and the increased risk has persisted in the era of drug-eluting stents. Previously, we have shown that local insulin treatment via periadventitial insulin application in Pluronic gels to retard insulin release can reduce neointimal hyperplasia after arterial injury in rats. We are now developing insulin-eluting stents that are coated with ionic polymers and insulin using a layer-by-layer technique in order to delay the endovascular release of insulin to an extent similar to that obtained with Pluronic gels. The release of the insulin-eluting stents (0.5U) was tested in vitro by placing the stents in phosphate buffer solution (PBS) at pH 7.4 and quantified using BioRad protein microplate assay. Next, the bioactivity of the insulin in the insulin-eluting stents (5U) was determined by subcutaneously implanting the stents in rats and determining their blood glucose. The insulin-eluting stents had a prolonged *in vitro* release of insulin that lasted for up to 8 hours. When the stents were implanted in rats, the insulin effect on blood glucose lasted for up to 2 hours, less than the action of 5U NPH, an intermediate-acting insulin that yielded a comparable glucose decline. We conclude that: 1) polymer bound insulin in stents is bioactive; and 2) its *in vivo* release is likely faster than the *in vitro* release. Therefore, further prolongation of insulin release is required before evaluation of the effect of our novel insulin-eluting stents on intima hyperplasia in animals.

2339-PO

The Effect of Metformine on the Hemoglobin Level of Type 2 Diabetes Patients

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Objective: To study the effects of metformin on the hemoglobin and erythrocyte levels in the patients with Type 2 Diabetes

Research Design and Methods: Baseline data from a clinical trial involving 400 drug naïve and metformin treated type 2 diabetic patients was analyzed. Before participating the clinical trial, The metformin treated patients received at least 3 months of metformin treatment at a minimum dose of 750 mg per day.

Results: The average erythrocyte levels of Metformine-treated patients and drug naïve patients were $4.61\pm0.54\times10^{12}$ and $4.78\pm0.52\times10^{12}$ ($p<0.000$), respectively. The average hemoglobin levels of Metformine-treated and drug naïve patients were 138.2±16.2g/l and 143.36±16.39g/l ($p<0.000$), respectively. The significant reduction of hemoglobin and erythrocyte levels in metformin treated group were still detectable after adjusting age, gender, BMI, course of disease, and baseline HbA1c ($R^2=0.223$ $p<0.000$). In the subgroup analysis, 99 patients treated with Metformine for less than six months showed the similar hemoglobin ($p=0.087$) and erythrocyte ($p=0.195$) levels to that of control group; while 301 patients treated with Metformine for more than 6 months showed significantly lower hemoglobin ($p<0.000$) and erythrocyte ($p<0.000$) levels than that of control group.

Conclusion: Metformine-treatment was associated with significant lower erythrocyte and hemoglobin level than non-Metformine-treated patients. The impact of this effect on using HbA1c to evalulate glycermic control in patients receiving metformin treatment and other health related issues need to be further explored.

2340-PO

The Effective Switch from Intensive Insulin Therapy to the Once-Daily GLP-1 Analogue Liraglutide in Patients with Fairly Well Controlled (HbA1c, 5.1-7.5%) Type 2 Diabetes

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GLP-1 improves hyperglycemia in a glucose-dependent fashion, but it has not been elucidated whether GLP-1 analogue is able to improve hyperglycemia effectively like insulin therapy in patients with fairly well controlled type 2 diabetes. We therefore investigated the efficacy and safety of the change to liraglutide from intensive insulin therapy in such patients. Inclusion criteria were adequate endogenous insulin secretion (urinary C-peptide > 40 μg/day) and controlled HbA1c levels of ≤ 7.5% on intensive insulin therapy with insulin dose of < 30 units. Eleven men and four women, aged 61.9 ± 7.8 years and with an HbA1c level of 6.4 ± 0.5% and a BMI of 24.4 ± 2.5 kg/m^2, were enrolled. Four times daily insulin injection therapy was discontinued, and then monotherapy with liraglutide was started. We performed statistic analyses in paired t test with the SPSS software. We examined serum metabolic markers and surveyed diabetes treatment satisfaction questionnaire (DTSQ) before and 12 weeks after switching. Body weight significantly decreased after 4 weeks of liraglutide treatment ($p < 0.01$), but rose moderately after 12 weeks ($p = 0.09$), compared with the baseline. HbA1c and BNP levels were significantly decreased after 12 weeks ($p < 0.01$, $p < 0.01$). There was a significant reduction of proinsulin to C-peptide ratio ($p = 0.02$). The DTSQ score revealed that the treatment satisfaction was significantly improved ($p < 0.01$), although mild digestive symptoms were observed in 60% of the subjects at the beginning of liraglutide administration. No participants discontinued this study, due to digestive symptoms. Symptomatic hypoglycemia and severe hypoglycemia recorded by SMBG were absent. In conclusion, when endogenous insulin secretion is preserved and intensive insulin therapy is performed with low insulin dose, the conversion from intensive insulin therapy to liraglutide monotherapy is considered to be an effective and safe therapeutic strategy even in patients with fairly well controlled type 2 diabetes. Of note, subjects were satisfied with liraglutide treatment despite mild digestive symptoms.

2341-PO

The Effects of Miglitol and Acarbose on Gastrointestinal Peptides Serection in Type 2 Diabetics

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Alpha glucosidase inhibitors (α-GI) such as miglitol and acarbose reduce the rate of carbohydrate digestion, and are especially used to postprandial hyperglycemia. Some recent researches showed that α-GI changes postprandial incretin levels.To investigate the effects of miglitol and acarbose on postprandial gastrointestinal peptides secretion, we performed crossover study. Nine type 2 Japanese diabetic patients (8 men, 59.1 ± 5.5 years, A1C 7.1 ± 0.2%) with only diet therapy or one oral hypoglycemic agent except for dipeptidyl peptidase-4 inhibitors were participated. Subjects were given miglitol (50mg), acarbose (100mg), or drug free just before 509 kcal breakfast containing 56% carbohydrate, 17% protein and 27% fat. The meal loads were tested 3 times within 4 weeks. Plasma glucose, insulin, active glucagon-like peptide-1 (aGLP-1), total gastric inhibitory polypeptide (GIP), glucagon, ghrelin, and des-acyl ghrelin (DG) were measured at before and after the meal (0, 30, 60, 90, 120, and 180 min). Single administration of miglitol or acarbose tended to reduce plasma glucose at 30-60 min after taking the meal compared to drug free. Plasma insulin and glucagon levels did not differ among miglitol, acarbose, and drug free. Since postprandial plasma ghrelin and DG levels fell, there was no difference among three conditions. Plasma aGLP-1 levels rose after the meal, and those of 60-90 min and 60 min were significantly higher than drug free in miglitol and acarbose, respectively.

Area under the curve (AUC) 0-180 min of aGLP-1 in miglitol was significantly greater than drug free. Plasma GIP levels rose after the meal, and those of 30-60 min and 30 min were significantly lower than drug free in miglitol and acarbose, respectively. AUC 0-180 min of GIP in miglitol was significantly lower than drug free. These changes of aGLP-1 and GIP secretion in α-GI administration are thought to be occurred by the alteration of reached digestive glucose to GLP-1 and GIP producing cells. Incretin secretion, however, was partly different between miglitol and acarbose. These differences may be occurred by absorption of the drugs and/or strength of inhibitory activity for a-glucosidase and amylase.

2342-PO

The Effects of Nateglinide and Acarbose on Glycemic Excursion in Standard Carbohydrate Meal Tests and Mixed-Meals in Drug Naïve Type 2 Diabetic Patients

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Nateglinide and Acarbose both specifically target postmeal plasma glucose with different hypoglycemic mechanisms. And postmeal plasma glucose excursion is directly linked to types of meals. This study aimed to compare the effects of Nateglinide and Acarbose on glycemic excursion, postmeal glucose profile in different types of meals: standard carbohydrate meal and mixed-meal.

For author disclosure information, see page 785.

A total of 20 drug naïve type 2 diabetic patients (11 female) aged 35 to 75 years old were enrolled. All subjects were randomized to receive Nateglinide, 120 mg three times daily (Na group, n=10) or Acarbose, 50 mg three times daily (Ac group, n=10) for 12 weeks. A 70g carbohydrate standard meal test and continuous glucose monitoring (CGM) over 3 consecutive days when patients ate mixed meals were performed at baseline and 12 weeks. The changes of blood glucose at 0, 15, 30, 60, 90 and 120 min after standard meal test, and the parameters including mean amplitude of glucose excursions (MAGE), absolute means of daily differences (MODD), largest amplitude of glycemic excursions (LAGE), and standard deviation of mean level of blood glucose fluctuation (SDBG) of CGMS between two groups were compared.

In carbohydrate meal: the postprandial glucose excursions (PPGEs) significantly decreased in both groups after 12 weeks therapy ($P<0.05$), while decreased more in Ac group than Na group (1.78±1.29 VS 1.23±0.65mmol/l, P=0.326). The 120min postprandial glucose decreased similarly (2.3±2.4 VS 2.1±1.9mmol/l, P=0.970) in both groups, while postprandial 30,60 min glucose decreased more in Ac group than Na group (30min:1.7±1.3 VS 0.2±1.6mmol/l, P=0.002; 60min: 3.3±1.7 VS 1.4±2.1mmol/l, P=0.005). In mixed meal: The parameters of CGMS in both groups had a trend to decline and declined more in Na group than Ac group, but the differences were not statistically significant.

Acarbose may be better at controlling early (30min, 60min) postmeal glucose and excursions in the patients who mainly consume carbohydrate meal than Nateglinide. While Nateglinide may be more suitable for patients who consume mixed (mainly contain protein and fat) meal.

2343-PO

WITHDRAWN

2344-PO

The Influence of Sedative-Hypnotic Agents on the Glycemic Control in Diabetic Patients Complicated with Insomnia

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To evaluate the influence of sedative-hypnotic agents on glycemic control in diabetic patients with insomnia, we studied 304 patients with type 2 diabetes(159 men; median age 65.8 years, median HbA1c 7.2%). We assessed the prevalence of insomnia, duration of sleep, usage of sedative-hypnotic agents, and their relationship with glycemic control. Patients were devided into three groups; A: those without insomnia, B: those with insomnia treated with sedative-hypnotic agents, C: those with insomnia untreated. The mean duration of sleep were A:7.2hrs, B:6.6hrs, C:5.5hrs and mean HbA1c were A: 7.0%, B: 7.1%, C: 7.9%. Significant differences were found among these three groups as to the duration of sleep and HbA1c. These data suggested that treatment of insomnia with sedative-hypnotic agents contributes to a better glycemic control.

2345-PO

The Intensive Management of Hyperglycaemia Is Less Likely in Non-Diabetic Patients Presenting to a Coronary Care Unit with Acute Coronary Syndrome

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Achieving normoglycaemia during Myocardial infarction has been shown to improve clinical outcomes. A variable insulin glucose protocol (VIG) was established to assist staff in a coronary care unit (CCU) to manage patients admitted with hyperglycaemia (glucose >11mmol/l) and acute coronary syndromes (ACS).The aim of this retrospective analysis was to assess the staff attitude, compliance and application of the VIG protocol in the management of hyperglycaemia in these patients during their admission in CCU.

A database of patients aged between 18 and 85years, admitted to the CCU with ACS and hyperglycaemia in a UK hospital between January and December 2007, were examined for the use of VIG. Patients with severe heart failure (NYHA IV) and severe renal failure (GFR<30) were excluded from the study.

106 patients (69% male), mean age 59years were identified. 66(62%) were not previously known diabetics (NkD) and of the 40 known diabetics, 16(40%) were on insulin. Only 53(50%) had VIG infusion commenced and of these only 10(20%) were NkD patients. None of these patients were referred to the diabetic team after 48hours of VIG infusion for consideration of long term insulin therapy. Only 13 NkD patients were referred to their primary care physician for post discharge glucose tolerance test and possible life style modification measures.

This study demonstrates that the use of the VIG protocol by staff in the CCU needs improvement. Crucially, NkD patients are less likely to be administered VIG and do not have their admitting hyperglycaemia communicated to primary care physicians. This could contribute to the higher in-patient and long term mortality already observed in this group of patients in several studies.

2346-PO

The Novel DPP-4 Inhibitor Linagliptin Is Associated with a Very Low Risk of Hypoglycemia: Results from a Large Phase III Program

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Patients with type 2 diabetes mellitus (T2DM) often do not reach treatment targets. A key reason for this is concern for hypoglycemia. This is of particular importance for vulnerable populations, such as elderly, obese, or renally impaired patients. Hence, a desirable requirement for novel therapies is to provide clinically meaningful efficacy while avoiding hypoglycemia.

An analysis of pooled primary data on 3572 patients with T2DM was conducted to evaluate hypoglycemic risk of the novel, oral dipeptidyl peptidase (DPP)-4 inhibitor linagliptin. Data from 8 randomized, placebo-controlled, Phase 3 clinical trials were pooled. Adverse events (AE) and investigator-defined hypoglycemia were evaluated. In addition, subgroup analyses were performed for elderly (>65 yr, n=902), obese (BMI ≥30, n=1286), and renally impaired (GFR <90 ml/min/1.73 m^2, n=1464) patients.

2523 patients received linagliptin 5 mg qd and 1049 patients received placebo. Overall, the incidence of AE and serious AE with linagliptin were similar to placebo (AE 55.8% vs 55.0%, serious AE 2.8% vs 2.7%). The hypoglycemic event rate was 8.2% with linagliptin and 5.1% with placebo. Notably, the 38% of patients on sulfonylurea (SU) background therapy accounted for 96% of all hypoglycemic events under linagliptin treatment. Similarly, 33% of patients receiving SU accounted for 87% of all hypoglycemic events under placebo. When patients were not on SU, the rate of hypoglycemic events with linagliptin was very low (<1%). A <1% hypoglycemic event rate with linagliptin was confirmed in the vulnerable subgroups of elderly, obese, and renally impaired patients when treated without SU background.

This pooled analysis from a large, global Phase 3 program shows that linagliptin is associated with a very low risk of hypoglycemia. When hypoglycemia occurred under linagliptin treatment or placebo, the vast majority of T2DM patients were also treated with SU. Thus, dose adjustment of SU should be considered when combined with a DPP-4 inhibitor.

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2347-PO

The Use of U500 Regular Insulin Via Continuous Subcutaneous Insulin Infusion (CSII): Clinical Practice Experience

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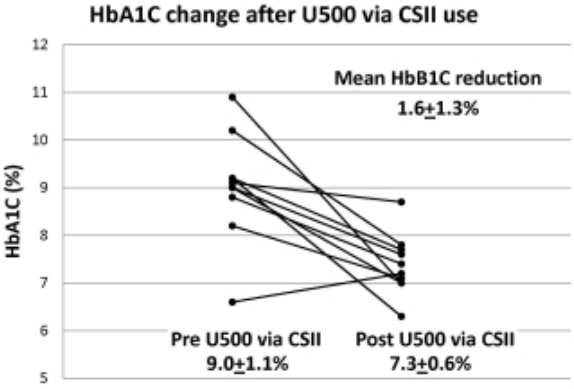
Achieving good glycemic control in diabetic patients with severe insulin resistance remains a clinical challenge. Short term studies using U500 regular insulin administered via CSII in such patients have recently been reported with encouraging results. In this study, we report our experience with U500 via CSII from two University Medical Centers.

We reviewed medical records from 10 patients using U500 via CSII in our clinics. The mean age was 45.5±10.9 yr with equal gender distribution. Eight subjects (80%) had type 2 diabetes, with one starting treatment during pregnancy, and two (20%) had type 1 diabetes. Baseline weight was 108±15.4 kg, and total daily insulin dose (TDD) was 234.2±111.4 units/d (2.2±0.9 units/kg/d). Prior to initiating U500 via CSII start, seven subjects (70%) were on multiple daily insulin injections, three (30%) were on CSII using insulin analogs, and five (50%) were using additional agent(s) (metformin, TZD and/or GLP-1 analogs). Mean baseline HbA1C was 9.0±1.1%, and duration of U500 CSII use was 31.8±28.1 mo (range 6-92 mo).

Mean HbA1C (%) after the start of U500 via CSII were as follows: 3mo,7.3±0.9(n=7); 6mo,7.5±1.0(n=9); 12mo, 7.7±0.7(n=8); 24mo, 8.0±1.0(n=4); 36mo,7.9±0.6(n=4); 48mo,8.1±0.6(n=2); and 60mo, 8.0±0.6(n=2). On average, subjects had a HbA1C reduction of 1.6±1.3% ($p<0.01$), without significant change in TDD (figure). Weight increased by 8.8±8.7 kg (p=0.01). There were

no reports of severe hypoglycemia, with exception of the pregnant patient with AM hypoglycemia despite overnight pump suspension.

In summary, use of U500 via CSII is effective in long term glycemic control in both type 1 and 2 insulin resistant diabetic subjects. However, the effect seems to be attenuated overtime, suggesting that ongoing pump adjustment may be necessary.



2348-PO

Time to BP Control in Diabetic Patients with Hypertension: Monotherapy, Free-Dose and Single-Pill Combinations

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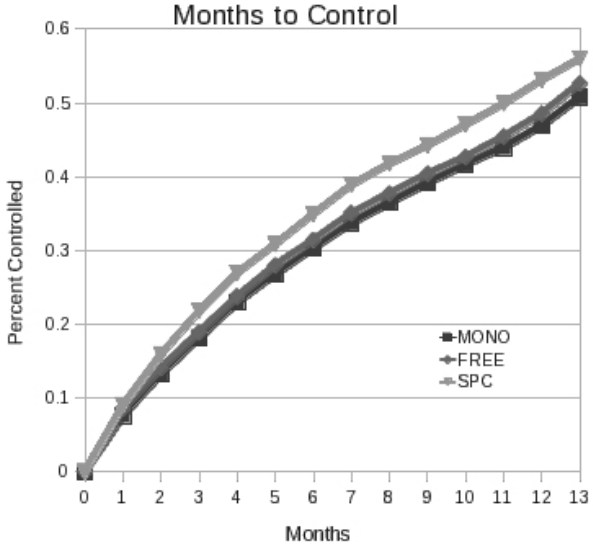
Background: Type 2 diabetes (T2D) and hypertension (HTN) double cardiovascular disease (CVD) risk vs. T2D or HTN only. Uncontrolled hypertensive patients at high risk for CVD experience fewer events when blood pressure (BP) is controlled more rapidly in the first year. Clinical efficacy trials document initial therapy with single-pill combinations (SPC) achieves more rapid BP control than monotherapy (MONO) with sequential add-on. And, adherence to SPC is better than to the same meds as free-dose combinations (FREE). OBJECTIVE: Determine the clinical effectiveness of initial therapy with MONO, FREE, or SPC for controlling BP in patients with HTN and T2D during the first year (13 mo) of treatment. METHODS: Electronic record system data were obtained from a community-based practice network; 27,991 patients with HTN and T2D were identified from Jan 2004 through Jun 2009 with T2D and BP that was ≥130/≥80 and untreated for ≥6 mo prior to initial therapy and who had ≥1 one year follow up data. Control was determined by the first follow-up visit with BP <130/<80. Multivariable proportional hazards regression (HR) was used to assess the independent relationship of initial treatment to BP control.



Results: '0' Months denotes initiation of SPC, FREE or MONO. Patients on initial SPC (N=2179) were 3–5 years younger and more likely to be women and have Stage 2 HTN than FREE (N=5,184) or MONO ([N=20,628] p<0.001). In multivariable HR adjusted for age, sex, initial BP, VA vs. non-VA care, and chronic kidney disease, initial SPC (HR 1.20, 95% CI [1.13–1.28]) was more likely to control BP than FREE (1.09 [1.04–1.13]) with both more likely to control BP than MONO (HR 1.00). CONCLUSION: In the first year of treatment, SPC is more effective for controlling HTN in T2D and may lower CVD risk more than FREE and MONO.

Supported by: Novartis

2349-PO

Ultra-Long-Acting Insulin Degludec: Two Different Formulations (U100 and U200) Are Bioequivalent and Show Similar Pharmacodynamics

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Insulin degludec (IDeg; formerly named SIBA) is a new basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in an ultra-long action profile. IDeg is being developed as two different formulations: a 100 U/ml (U100) formulation and a 200U/ml (U200) formulation (to allow the administration of larger doses from a pre-filled insulin delivery system with fewer injections).

This double-blind, two-period, cross-over trial characterized the pharmacodynamic response to U100 and U200 at steady-state. Subjects with type 1 diabetes (n=33; mean: 40 ± 10 yrs old, diabetes duration 20 ± 11 yrs, A1C 7.3 ± 0.8%, C-peptide <0.3 nmol/l) were randomized to 0.4 U/kg U100 or U200 once daily for 8 days. On Day 8, a glucose clamp procedure was performed whereby euglycemia was established and maintained at 5.5 mmol/l by a variable iv glucose infusion over a period of 5 hours. After injection of U100 or U200, subjects were maintained in the clamp for 26 hours.

Glucose infusion rates (GIR) were comparable for U100 and U200 (AUC_{GIR} [mg/kg]: 2255 vs. 2123). The mean ratio of U200/U100 for the primary endpoint ($AUC_{GIR,t,SS}$) was 0.94 [95% CI: 0.86; 1.03]. In a post-hoc analysis, bioequivalence was established between U100 and U200 as the 90% confidence intervals of the ratios (U200/U100) for $AUC_{IDeg,\tau,SS}$ and $C_{max,IDeg,SS}$ were within the interval 0.80–1.25 (see Table 1). Both formulations were well-tolerated with no marked differences in the distribution of adverse or hypoglycemic events.

In summary, the U100 and U200 insulin degludec formulations are bioequivalent and show similar pharmacodynamics at steady-state, suggesting that U100 and U200 can be used interchangeably in clinical practice.

Table 1. Statistical Analyses for Bioequivalence

	U200	U100	Ratio [90% CI]
$AUC_{IDeg,\tau,SS}$ (pmol*h/l)	110925†	112236†	0.99 [0.91; 1.07]
$C_{max,IDeg,SS}$ (pmol/l)	6073†	6559†	0.93 [0.84; 1.02]

†means derived from ANOVA model with treatment and period as fixed effects, subject as random effect.

2350-PO

Urinary Metanephrine-Normetanephrine Ratio Is an Indicator for the Efficacy of Sitagliptin in Type 2 Diabetics

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Dipeptidyl peptidase-4 enzyme (DPP-4) inhibitors prolong the action of incretins, and lead to increased insulin secretion and reduced hepatic glucose production. Sitagliptin is a first approved DPP-4 inhibitor for the management of type 2 diabetics (T2D) in Japan. It has been reported that catecholamines such as epinephrine affect insulin secretion and hepatic glucose production. The aim of this study is if there is relationship between intrinsic catecholamines and the efficacy of sitagliptin during treatment of T2D. Thirty eight of Japanese T2D (HbA1c>6.9%) having visit my clinic over a half year were treated with 50 mg/day of sitagliptin for 12 weeks. Depending on the degree of reduction in HbA1c after 12 weeks of treatment (ΔHbA1c), patients were divided into 3 groups of non-responders (ΔHbA1c<0.3), responders (0.3≤ΔHbA1c<1.5) and marked responders (1.5≤ΔHbA1c).

For author disclosure information, see page 785.

	All	non-responders	responders	marked responders
numbers	38	11	26	9
age(years)	60.1±13.6	62.5±18.2	60.6±9.8	60.5±11.6
male/female	29/9	8/3	23/3	6/3
body-mass index	25.5±3.4	26.6±3.8	25.4±2.6	23.8±2.8
HbA1c (%)	7.89±0.78	7.71±0.88	7.75±0.76	8.35±1.95
metanephrine (mg/gram creatinine)	0.09±0.04	0.09±0.04	0.09±0.03	0.14±0.05
normetanephrine (mg/gram creatinine)	0.23±0.11	0.26±0.14	0.23±0.11	0.17±0.05
normetanephrine/ metanephrine	2.71±1.32	3.06 ±1.43	2.83±1.22	1.26±0.19*

*, P<0.05 compared to the values in responders and marked responders

Interestingly, urinary metanephrine-normetanephrine ratio in the marked responder group was significantly ($P < 0.05$) lower than that in responder group as shown in table. Since metanephrines and normetanephrine are metabolites of epinephrine and norepinephrine respectively, urinary metanephrines and normetanephrine reflected production levels of epinephrine and norepinephrine respectively. Epinephrine activates both of α and β adrenergic receptors. On the other hand norepinephrine does not stimulate β adrenergic receptor. Low urinary metanephrine-normetanephrine ratio may mean that β adrenergic action is dominant and is responsible to response to sitagliptin in the marked responder group.

2351-PO

Use of Clinical Microsystem Methodology To Improve Glycemic Control in Hospitalized Patients with Type 2 Diabetes

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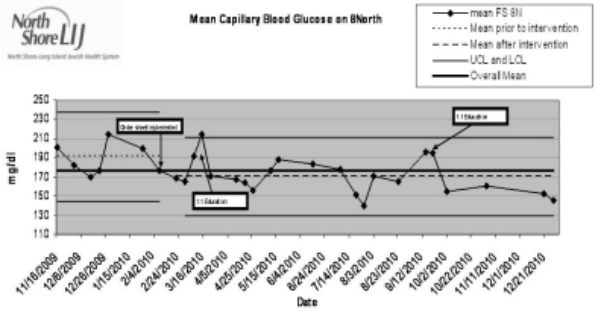
Nationally, patients with diabetes mellitus constitute 25% of those hospitalized. At Long Island Jewish Medical Center, a multi-ethnic urban facility, inpatients with diabetes constitute 39-66% of patients. Many of these patients are newly diagnosed with diabetes on admission.

Hyperglycemia in this population has been associated with increased morbidity, mortality, lengths of stay and health care costs, even beyond that seen in patients with known diabetes. While evidence is lacking for very tight glycemic control in the non-critically ill, the consensus is that moderately good control is required to prevent poor outcomes. The preferred method for achieving this, is basal-bolus insulin, rather than traditional "sliding scale" insulin therapy.

We used the Clinical Microsystem Methodology developed by Nelson, et. al 2003 to design and implement improved glycemic control for Type 2 diabetes patients on a 37 bed medical unit. Data on percent of patients with diabetes and the level of pre meal glucose control was collected on a regular basis prior to, during and after the intervention. The intervention consisted of the introduction of a newly designed basal-bolus insulin order sheet. Education of physicians, NPs and PAs, and RNs around the new order sheet was a critical component of the intervention.

The data are displayed in a continuous run chart in Figure 1.



The introduction of a new insulin order sheet in addition to education about basal-bolus insulin therapy showed significant improvements in mean capillary blood glucose levels. The average of mean premeal glucose levels improved from 191 to 171 after the above interventions. Based on this success, basal-bolus insulin therapy was intiated hospital-wide. The variability seen after intervention was met with continuing education. This remains important as we continue to improve glycemic control.

2352-PO

Use of Vascular Protection Therapies in the Prevention and Management of Diabetes Complications in Low- to Middle-Income Countries: Findings from the A_1chieve Study

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Few comparative data are available on the prevention and management of the long-term complications in type 2 diabetes mellitus in routine care around the globe. A_1chieve is a multinational, observational study in people starting insulin analog therapy in 28 countries across Asia, Africa, Europe and Latin America. Data are reported here for therapy other than glucose-lowering therapies in 65 685 people (age 54±12 [±SD] years, 56% male, duration of diabetes 9±7 years). Data on diabetes complications were not available from the responsible clinician in 1% to 30% of people in different regions, suggesting defective complications surveillance. Overall only 37% of people were taking a statin, this being highest in those with a previous cardiovascular disease (CVD) (62%). Statin use was lowest in people in China with (48%) or without (19%) CVD, but not above 75% and 47% respectively in any region. Aspirin use tended to be higher than statin use, notably in China where it was closer to the overall usage, 75% and 31% in people with or without CVD respectively. A renin-angiotensin system (RAS) blocker (angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker) was used by 43% of all people, but 76% of those with prior CVD, and by 60% of those with documented microvascular complications. RAS blocker use reached 88% of people with microvascular complications in Russia, but only 41% in China. We conclude that, in people starting insulin, use of vascular protective agents is higher than anticipated from historical data, but globally still appears to be short of guideline recommendations, particularly in China.

Table. Use of vascular preventative drugs (%) in people with type 2 diabetes mellitus starting insulin

	Total population	CV disease		Microvascular complications		Neither type of complication
		Present	Absent	Present	Absent	
RAS blocker	42.6	75.7	30.5	60.1	22.7	17.0
Aspirin	42.6	75.0	31.3	58.3	25.8	20.2
Statin	37.2	62.1	29.1	50.6	23.7	19.1

Data available for drugs and complications in >53 700 people in all medication categories. CV, cardiovascular; RAS, renin-angiotensin system

2353-PO

Variations in Tissue Selectivity amongst Insulin Secretagogues: A Systematic Review

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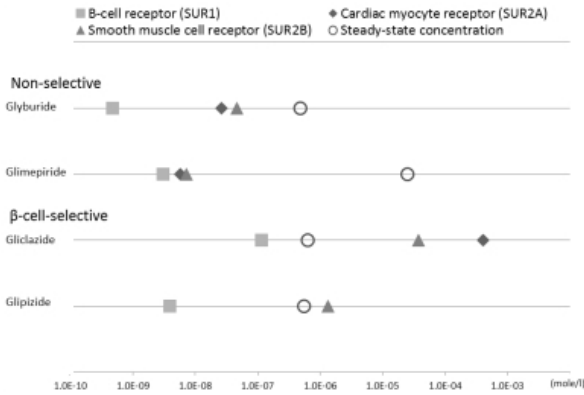
Insulin secretagogues promote insulin release by binding to sulfonylurea receptors (SUR1) on the β-cell. However, these drugs can also bind to SUR2A and SUR2B isoforms on cardiac myocytes and smooth muscle cells. Binding to SUR2A and SUR2B possibly blocks ischemic preconditioning, an endogenous protective mechanism enabling cardiac myocytes to survive periods of ischemia. This study was designed to identify insulin secretagogues that selectively bind to SUR1 when given at usual therapeutic doses. Using standard systematic review methods, we searched three electronic databases from inception to 30 September 2010. Original experimental studies were included if they measured SUR binding affinity of an insulin secretagogue using standard electrophysiological techniques. Experimental conditions, SURx and Kir6.x sources, and the half-maximal inhibitory concentration (IC_{50}) were collected. Phase 1 or 2 clinical trial data were used to determine steady state concentrations (C_{ss}) for each drug in humans. We identified 27 studies (14 insulin secretagogues) reporting the IC_{50} value for ≥1 SUR isoforms. Insulin secretagogues can be divided into two groups based on binding affinities to SURx isoforms.



Some drugs (gliclazide) have a wide gap between observed binding affinities for SUR1 and SUR2A/SUR2B, while others (glimepiride) have similar, overlapping binding affinities for all three isoforms. When the C_{ss} for these drugs is considered, gliclazide may selectively bind to SUR1, while glimepiride would bind to all three isoforms at therapeutic doses. This review illustrates wide variation in SUR binding affinity characteristics amongst insulin secretagogues, which may be augmented by their pharmacokinetic properties. The differences in tissue selectivity may translate into different levels of adverse cardiovascular risk amongst the insulin secretagogues.

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Clinical Diabetes/ Therapeutics PUBLISHED ONLY

2354-PO

What Characteristics at Baseline Are Associated with the Glucose-Lowering Effect of Colestimide in Patients with Type 2 Diabetes with Hypercholesterolemia?

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We have previously reported that colestimide, an anion exchange resin, improved glycemic control in patients with type 2 diabetes. However, no studies of the glucose-lowering effects of colestimide have been undertaken to identify responders and in non-responders. In this study, we compared glycemic control, lipids and body mass index (BMI) between groups receiving colestimide (n=59) and statins (n=46) until 24 weeks after the commencement of treatment. Furthermore, the glucose-lowering effect of colestimide on response (n=51) was defined by a 15% decrease or more in glycated hemoglobin A1c (A1c) or a 20% decrease or more in plasma glucose level after 24 weeks. Nonresponders (n=8) were defined as patients who did not meet this criterion. In the responder group, fasting plasma glucose (FPG) decreased significantly from 10.23±4.88 to 7.16±2.72 mmol/L after 24 weeks (P<0.001), and A1c declined from 8.8±1.9% to 7.1±1.1% (P<0.001). In the nonresponder group and statin group, FPG and A1c did not change. Multivariate analysis revealed that baseline A1c and the presence of cholelithiasis were the significant determinants of the colestimide treatment after adjustment for age, gender and baseline total cholesterol levels. Moreover, multivariate analysis revealed that baseline A1c and BMI were the significant determinants of the responder or nonresponder associated with colestimide treatment after adjustment for age, gender and baseline total cholesterol levels. In conclusion, baseline A1c and the presence of cholelithiasis have a strong and independent influence on the glucose-lowering effect of colestimide.

CLINICAL THERAPEUTICS/NEW TECHNOLOGY—TREATMENT OF INSULIN RESISTANCE

2355-PO

Barley β-Glucan Beverage Improves Insulin Sensitivity in Individuals at High Risk for Diabetes Mellitus

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Prior studies suggest soluble fibers may have favorable effects upon glucose metabolism. This prospective, intent-to-treat, randomized, placebo controlled, double blind, parallel group trial evaluated 50 subjects (45 completers) administered placebo (control), low dose (3 g/d) barley B-glucan (BBG; Barliv™), or high dose (6 g/d) BBG. Subjects (68% female) had a mean age of 56 years, BMI 32 kg/m^2 and baseline fasting plasma glucose 102 mg/dl without prior diagnosis of diabetes mellitus. All subjects followed a weight-maintaining Therapeutic Lifestyle Change diet and consumed three 11 oz test beverages every day with meals for 12 weeks. The primary endpoint measures were fasting and post-oral glucose tolerance testing (OGTT), plasma glucose and insulin.

Table 1. Changes in glucose, insulin and insulin resistance levels after 12 weeks

Group	N[a]	Fasting glucose (mg/dl)	Fasting insulin (uIU/ml)	HOMA-IR[b]	Glucose iAUC[c] (mg/dl*min)	Insulin: iAUC (uIU/ml*min)
Placebo	17	7.64	2.07	0.68	1234	134
3 g/d BBG	16	8.25	7.81	3.43	-1775	843
6 g/d BBG	17	1.19	-1.50	-0.35	-76	-59
P values[d]		NS	3 g/d: 0.339; 6 g/d: 0.006	3 g/d: 0.440; 6 g/d: 0.013	3 g/d: 0.012; 6 g/d: 0.366	NS

[a] N=Number of subjects; NS=not significant [b] HOMA-IR=Homeostasis Model Assessment of Insulin Resistance [fasting glucose (mg/dl) x fasting insulin (uU/mL)/405] [c] iAUC=incremental Area under the curve [d] Pairwise comparisons to placebo (Dunnett's procedure) where overall ANOVA (analysis of variance) indicated a statistically significant difference across all treatments.

The 3 g/d BBG group had significantly reduced glucose iAUC during OGTT compared to the placebo group. The 6 g/d BBG group had significantly reduced fasting insulin and HOMA-IR compared to the placebo group. Beverages were generally well tolerated with no serious adverse experiences and no differences between groups for adverse events. These findings suggest 6g/d BBG beverage consumed over 12 weeks can improve insulin sensitivity among generally healthy, hyperglycemic individuals who have no prior diagnosis of diabetes mellitus.

Supported by: Cargill, Inc.

2356-PO

Biomarker Pattern Analysis and Tolerability of Ginkgo Biloba (EGb 761) in Point-of-Care Theranostics of Metabolic Syndrome Patients

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We had reported on the beneficial effects of Ginkgo (EGb 761, 2×120 mg/dL) on arteriosclerotic nanoplaque formation and size in high-risk patients after an aortocoronary bypass operation. With the present 2-month clinical trial, we intended to confirm these effects in 11 patients with metabolic syndrome. A novel biomarker spectrum embracing parameters of plaque formation, stability and progression, oxidative stress, inflammation, lipid composition and second messengers, made point-of-care theranostics feasible. Nanotechnologic biosensor ellipsometry, photometric methods, ELISAs and EIAs were applied. The reduction of nanoplaque formation amounted to 14.3±2.9% (p<0.0077) and of nanoplaque size to 23.4±3.7% (p<0.0004). Results for other biomarkers are collected in the table. Since none of the patients had a manifest diabetes, we evaluated insulin resistance. Fasting morning glucose was reduced from 94.4 to 90.2 mg/dL (p<0.0291), insulin from 12.7 to 11.5 mU/L (p<0.042), and HOMA-IR from 3.07 to 2.64 mU/L×mg/dL (p<0.0244). Because ginkgo is not an antidiabeticum, we looked out for a mechanistic explanation. Insulin was correlated to IL-6, hs-CRP and TNFα, as known from large clinical trials. Remarkable effects were measured: reduction of nanoplaque formation and size; upregulation in radical scavenging enzymes SOD/GPx; attenuation of oxLDL/LDL and Lp(a); increase in vasodilatory cAMP/cGMP and decrease in vasoconstrictory 8-*iso*-$PGF_{2\alpha}$ and MPO, removing endothelial dysfunction; insulin resistance was diminished. Since ginkgo was tolerated without any side-effects, it may be used as complementary drug in the treatment of metabolic syndrome and diabetic patients.

	before	after	change [%]	error probability
SOD [U/mL]	126.2±9.0	146.2±11.4	+17.7	<0.0095
oxLDL/LDL [U/g]	65.1±3.0	50.7±2.4	-21.0	<0.0020
8-*iso*-$PGF_{2\alpha}$ [nmol/L]	24.9±4.6	15.0±2.0	-39.8	<0.0027
MPO [ng/mL]	60.4±7.8	41.1±7.7	-29.6	<0.0137
IL-6 [pg/mL]	3.0±0.5	2.6±0.5	-12.9	<0.0407
Lp(a) [mg/dL]	50.8±7.3	39.5±6.3	-26.3	<0.0010
hs-CRP [mg/L]	8.9±4.1	4.9±2.5	-39.3	<0.0049
cAMP [nmol/L]	40.3±3.8	54.5±3.4	+43.5	<0.0010
cGMP [nmol/L]	8.5±0.5	10.9±0.5	+32.9	<0.0010

For author disclosure information, see page 785.

ADA-Funded Research

2357-PO

Change in Antihypertensive Medication Dose Following Initiation of Liraglutide in Patients with Type 2 Diabetes Mellitus: A Real Life Clinical Experience

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GLP-1 analogues like liraglutide are known to reduce systolic blood pressure (SBP) in patients with type 2 diabetes. Reduction in SBP is not related to concurrent antihypertensive medication.

The present case series shows data of nine type 2 diabetes patients with hypertension who have completed at least 12 weeks of treatment with liraglutide 1.2 mg/day. Baseline characteristics: mean age - 48.4±3.5 years; mean duration of diabetes - 10.2±2.8 years; mean BMI- 33.4±3.0 kg/m^2; mean HbA1c - 7.7%; mean SBP - 140.5±7.8 mmHg and diastolic blood pressure (DBP) - 86.7±3.5 mmHg.

In comparison to baseline, Liraglutide treatment reduced mean HbA1c by 1.0±0.8%, body weight by 6.3±3.1 kg and mean BMI by 2.3±1.4 kg/m^2. Liraglutide also reduced both SBP and DBP in all patients.

Table 1

Patient number	Baseline	Follow-up 1	Follow-up 2
1	144/88	134/90	115/85
2	157/86	132/82	112/78
3	130/77	125/77	112/70
4	134/80	121/72	110/72
5	144/81	128/78	121/70
6	142/81	123/79	110/75
7	138/66	130/68	110/57
8	135/75	130/72	118/72
9	141/82	129/70	120/69

SBP and DBP were reduced by 26.3±8.6mmHg (p<0.01) and 12.8±6.7mmHg (p<0.01) respectively. Contrary to the previously published reports, median pulse rate reduced from 88/min to 72/min. During the same period, the total daily dose of antihypertensive was significantly reduced (p<0.05).

Table 2

Patient Number	Type of ARBs Used	Total Daily Dose at Baseline (mg)	Total Daily dose at Follow-up visit 1 (Week 6) (mg)	Total Daily Dose at Follow-up visit 2 (Week 12) (mg)
1	Telmisartan Hydrochlorothiazide	80 25	40 12.5	20s 6.75
2	Telmisartan	40	20	10
3	Telmisartan	20	10	5
4	Telmisartan	40	20	10
5	Telmisartan Hydrochlorothiazide	80 25	40 12.5	20 6.75
6	Losartan	100	50	12.5
7	Telmisartan	40	40	10
8	Telmisartan	40	20	10
9	Telmisartan	80	40	20

Three subjects had giddiness and two patients experienced nausea.

In this real-life practice data, liraglutide reduced both systolic and diastolic blood pressure along with improvement in HbA1c. Treating clinicians need to consider this potential benefit and adjust the dose of anti-hypertensive medications accordingly.

2358-PO

Impact of Postpartum Lifestyle and Pharmacological Intervention on Metabolic Profiles in Women with Prior Gestational Diabetes at 1 Year Followup

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We investigated the impact of lifestyle and medical intervention on the progression of metabolic disorders in 69 women with prior gestational diabetes mellitus (p-GDM) first assessed at 6-12 weeks postpartum. Adherence to follow-up was 68%; 47 p-GDM women completed a repeat 75-g oral glucose tolerance test and metabolic assessment at 1 year postpartum.

The overall incidence of metabolic dysfunction in all p-GDM women at 6-12 weeks postpartum was 47%. All were recommended for medical therapy, 35% chose lifestyle counseling only.

At 1 year follow up, metabolic dysfunction was significantly increased to 63% in the lifestyle only group, 26% had dysglycemia and 37% had impaired β-cell function. Medical intervention led to significant improvement with no dysglycemia and 25% with β-cell dysfunction. All drug-treated p-GDM women had a less atherogenic profile while no change in the lipid profile was seen with lifestyle intervention.

Parameter	Lifestyle		Medical		p-value
	Postpartum	1 year	Postpartum	1 year	
Dysglycemia (%)	5	26	50	0	<.05
Metabolic Dysfunction (%)	35	63	100	25	<.003
TRG/HDL ratio	2.5 (.3)	2.6 (.6)	4.7 (9.7)	2.5 (9.6)	<.01

The BMI steadily increased from prepregnancy to 1 year follow-up with lifestyle whereas there was a significant decrease in postpartum BMI with medical therapy at the 1 year visit.

Parameter	Lifestyle			Medical			p-value
	Pre-	Postpartum	1 year	pre-	Postpartum	1 year	
BMI (kg/m2)	27.2 (1.1)	27.8 (1.1)	28 (1.2)	27.8 (2.4)	29.5 (.5)	27.5 (2.6)	<.018

Women with p-GDM are at high risk for developing carbohydrate intolerance and atherogenic lipid profiles. The most obvious reason for the progressive metabolic derangement of glucose tolerance is the increase in BMI after index pregnancy found in the present study. Although most p-GDM women were concerned about developing overt diabetes, only a few had changed their lifestyle and/or lost weight after pregnancy. This indicates that lifestyle instruction needs to be much more frequent and intensive in the period after pregnancy. Promising results have been achieved by combining lifestyle counseling with pharmacotherapy.

Supported by: BCBSLA and Pennington Foundation

2359-PO

WITHDRAWN

2360-PO

The Effect of Testosterone Replacement on Glycemic Control in Hypogonadal Men with Type 2 Diabetes Mellitus

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The objective of this study was to examine the effect of testosterone replacement therapy on blood sugar control, measured by HbA1c, in hypogonadal men with type 2 diabetes mellitus (DM2).

This is a historical prospective and longitudinal study. We have assessed the laboratory results of 639 individuals retrieved from the electronic medical record system of Hines VA Hospital. The study was approved by the institutional Human Studies Sub Committee. A specific exclusion criterion was used to eliminate patients suffering from variety of diseases that could have influenced blood sugar control. The subjects with DM2 and hypogonadism were divided into two experimental groups. The treatment group (n=81) had received testosterone therapy for 6 months to 10 years and control group (n=52) who deferred testosterone therapy based on some personal preferences. HbA1C was checked every 3 months. The data was analyzed using a longitudinal model with two random effects.

There is a modest significant difference of HbA1c (p=0.05) between the two experimental groups over time after adjusting for both HbA1c at baseline and population time trend of HbA1C level. There is a 0.247% differences on the percentage of HbA1c between the 2 groups.

In conclusion, testosterone therapy has improved blood sugar control in hypogonadal subjects with type 2 diabetes mellitus.

2361-PO

The Effects of Pinitol on the Glucose Level, Insulin Resistance and the Adipocytokine Levels in Patients Who Are in a Prediabetic State

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Pinitol is thought to improve insulin resistance. We performed this study to evaluate the effects of pinitol on the glucose level, insulin resistance and the adipocytokine levels in subjects with pre-diabetes.

A total of 22 subjects with pre-diabetes was enrolled. The subjects were randomized to receive pinitol (n=12) or placebo (n=10) for 12 weeks. The clinical and laboratory parameters were assessed for all the participants.

There was no significant difference of the mean change in the levels of glucose, HbA1c, insulin and HOMA-IR between the pinitol and control groups at the end of 12 weeks treatment. The mean increment of the adiponectin level was significantly higher in the pinitol group than that in the control group. There was also no difference of the mean change in the level of leptin and RBP-4 between the two groups.

As a conclusion, twelve weeks treatment with pinitol was effective on increasing the adiponectin level, but it had no effect on the glucose level, insulin resistance and the levels of other adipocytokines in the subjects with pre-diabetes.

2362-PO

Use of a Controlled Fast for the Treatment of Severe Insulin Resistance in Patients with Type 2 Diabetes

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Patients with type 2 diabetes and severe insulin resistance often require large doses of insulin therapy to achieve target glycemic control. As insulin dose increases over time, patients may have decreased benefits with treatment, as well as unfavorable metabolic side effects such as weight gain and increased hunger. The purpose of this IRB-approved study is to describe our experience on the effect of a controlled, prolonged fast on insulin requirements, hyperglycemic control, and weight loss in patients with type 2 diabetes and severe insulin resistance. A total of 15 patients completed a controlled, prolonged fast consisting of carb-free clear liquids for the treatment of severe insulin resistance. Insulin was reduced by 50% in the first 36 hours and then adjusted individually. Pre-fast and post-fast (up to 6 months) data was collected assessing the effects on HbA1C, total insulin requirements, weight, and BMI. A total of 18 fasts were completed by the 15 patients. The majority were 72 hours in length (13), 3 were 60 hours, 1 was 48 hours, and 1 was 96 hours. Two of the fasts were observed in the hospital, while the remainder occurred at home under the medical supervision of a physician. The mean HbA1C was 9.95% prior to the fast and reduced to 9.14% at 1 month post-fast and 9.20% at 2-6 months post-fast. The mean insulin requirements were 275 units prior to the fast, 132 units at 2 weeks post-fast, 144 units at 1 month post-fast, and 201 units at 2-6 months post-fast. The mean weight was 266 pounds prior to the fast, 258 pounds at 2 weeks post-fast, 251 pounds at 1 month post-fast, and 242 pounds at 2-6 months post-fast. The mean BMI was 39.7 prior to the fast, 38.3 at 2 weeks post-fast, 37.5 at 1 month post-fast, and 34.9 at 2-6 months post-fast. There were 2 episodes of mild hypoglycemia reported, neither of which required medical intervention. Based on our findings, patients with type 2 diabetes and severe insulin resistance can be treated safely at home with a prolonged, controlled fast to achieve better glycemic control on smaller doses of insulin with continued weight loss and reduction in BMI.

HEALTH CARE DELIVERY/ECONOMICS

2363-PO

A Comparison of Insulin Adherence in Patients with Type 2 Diabetes Initiating Therapy with Insulin Detemir in a Pen Device or NPH Insulin in a Vial

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Non-adherence to insulin in patients with type 2 diabetes represents a serious challenge for health care providers. Some potential explanations for non adherence are aversion to injection and risk of hypoglycemic events. In clinical trials, insulin analogs have shown to reduce the risk of hypoglycemic events versus human insulins. In addition, a recent review suggested that insulin delivered via a pen device may result in greater medication adherence versus insulin delivered via vial and syringe. This study was conducted to compare the adherence rates for patients initiating basal insulin therapy with insulin detemir(IDet) in a pen device (FlexPen®) versus those initiating therapy with NPH insulin via vial and syringe.

Data were gathered from a large US national payer retrospective claims database, and included only patients with type 2 diabetes that initiated insulin therapy with either IDet FlexPen® or NPH in vials. Patients were excluded if they had evidence of any previous insulin use in the 12-month pre-index period. Patients with claims for any other type of insulin, other than the index insulin during the 12-month observation period were also excluded. Patients were defined as being adherent to therapy if they had an MPR of at least .80 in the 12-month follow up period.

The IDet FlexPen® cohort (n=1082) and the NPH vial cohort (n=794) were of similar age (54.06 vs. 53.13, p=0.134); however, the IDet FlexPen® cohort had a lower proportion of female patients (44% vs. 55%, p<0.001) and fewer treatment naïve patients (no pre-index OADs) (9% vs 45%, p<.001), than the NPH vial cohort. After controlling for important confounders, patients initiating insulin therapy with IDet FlexPen® had a 39% higher adjusted odds of achieving an MPR of 0.80 versus patients initiating insulin therapy with NPH vial (OR 1.385, 95% CI 1.037-1.849).

These results suggest that adherence may be improved for patients initiating basal insulin therapy with IDet in the FlexPen® versus NPH in a vial.

Supported by: Novo Nordisk

2364-PO

A Follow-Up Study on Diabetes Care after Implematng Quality Improvement Measures in a Family Medicine Residency

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The goal of this study is to evaluate the impact of diabetes care in the Family Medicine Clinic at San Joaquin General Hospital, after quality improvement (QI) measures was implemented for six months.

We conducted a retrospective study of randomly identified diabetic charts that met the study inclusion criteria. Residents reviewed the charts and collected the data by a modified AAFP METRIC Diabetes data collection sheet. The results were compared to the previous data collected in the 2009 METRIC Diabetes study. P-value was used to determine statistical significance.

Study inclusion criteria: 1) Adult ≥18 years of age seen at the Family Medicine Clinic for more than two visits during the last six months following the implementation of diabetes QI interventions 2) Adults ≥18 years with a diagnosis of Diabetes Mellitus with ICD9 code 250.00 or 250.02. QI measures include: 1) A customized stamp that reminds provider to order appropriate test, eye exam and immunization 2) Diabetic management tools were made available in exam rooms. A total of 95 diabetic charts were reviewed and compared with the previous study of 120 charts.

We found that retinal screening increased by 10%. Monitoring of diabetic care measure (i.e. lipid panel, HgbA1c, urine microalbumin), and preventive care (vaccinations and foot exam) did not improve. 52% of the studied patients were taking oral therapy alone; 40% used insulin alone, and 8% were treated with combined insulin and oral therapy. HbA1c (7.0-7.9) increased by 6 %, HbA1c (9.0-9.9) decreased by 6%. 76% took statins and 85% are on angiotensin converting enzyme inhibitors (ACEI). 79% had total cholesterol <200 and 67% had LDL <100. (7% and 12% improvement comparing to the previous study; p=0.28. p=0.12 respectively).

After six months of implementing QI measures, no significant statistical improvement of diabetes care was found. However, encouraging trend of improvement was seen with HbA1c, total cholesterol and lipid panel. We concluded that six months of implementation may not be long enough to demonstrate measurable improvement in a small study. We plan to repeat the study in 12 months.

2365-PO

An Analysis of Healthcare Engagement in Patients with Diabetes

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While the financial impact of healthcare resource utilization in patients with diabetes has been studied, we present an analysis of healthcare engagement for patients with diabetes. This retrospective cohort study evaluates visit and non-visit encounters for adult patients with and without diabetes receiving primary care at a large academic medical center.

The cohort included all patients who had at least one routine primary care visit in the year prior to the follow-up period 1/1/2008 through 12/31/2009. Data were collected through an established patient care registry. Patients with diabetes were identified using a previously validated algorithm which included ICD-9 codes, medications and glucose values. All clinic visits and clinical communications (provider notifications, nurses' notes, appointment communications, prescriptions and orders) were captured during the follow-up period. Annualized rates of visit and non-visit encounters were calculated for patients with and without diabetes. Age, gender and race adjusted rate ratios of visit and non-visit encounters were compared using Poisson regression analysis for the 2-year period.

There were 1373 patients with diabetes and 8683 patients without diabetes. Patients with diabetes were less likely female (54% vs. 57% respectively); more likely to be of black race (27% vs. 12%) and of older age with median of

For author disclosure information, see page 785.

62 years (IQR: 53, 73) in diabetes patients and 54 years (IQR: 43, 66) in non-diabetes patients. The rates of visit and non-visit encounters were 13.7 and 30.3 for patients with diabetes. For non-diabetes patients, the rates were 9.0 and 17.4. These differences remained after adjustments for age, gender and race. Patients with diabetes had a 27% higher rate of face-to-face encounters with healthcare providers during the study period (adjusted RR= 1.27, 95% CI: 1.22, 1.32). Patients with diabetes also had a 42% higher rate of non-visit encounters (adjusted RR=1.42, 95% CI: 1.37, 1.48).

We have quantified the increased engagement with the healthcare system experienced by patients with diabetes. For the first time, we have provided an estimate of non-face-to-face engagement.

2366-PO

Are We Missing the "Lean"?

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Impaired fasting glucose (IFG) predisposes one to a greater risk of developing type 2 diabetes(T2DM) and an even greater risk of cardiovascular disease. The progression from IFG to T2DM, as demonstrated by The Diabetes Prevention Project, can be delayed/prevented by either lifestyle/pharmacological intervention. Thus, early diabetes screening to raise awareness of risk and intervention to change lifestyle is key to successful prevention of T2DM. However, the present ADA guidelines recommend screening for asymptomatic diabetes in all adults who are overweight/obese (BMI :≥25kg/m^2) and present with additional risk factors as listed in the Standards of Medical Care Guidelines or achieve the age of 45 years. The purpose of this study is to determine the point prevalence of young adults, 18 to 29 years of age(a group that is typically uninsured and has less health care professional yearly encounters) with a Body Mass Index (<25 kg/m^2) and IFG (fasting glucose:100mg/dl- 125mg/dl) using the national NHANES (2007-2008) dataset. There were 1,191 NHANES participants in the 18-29 year old age group, of which 468(males=52.6%, females= 43.8%) had fasting glucose results. From this group (n=468), 54(12%) participants (48=males,6=females) met the following inclusion criteria; BMI<25kg/m^2 ("lean group")andfasting glucose between 100mg/dl-125mg/dl. Thirty-three percent of the males and 17% of the females were Caucasian while 27% (males) and 50% (females) were Mexican-American .Ninety percent (n=43) of the males and 100% (n=6)of the females responded "no" when asked if they had ever been told by a health care professional that they had a risk for developing diabetes, whereas 100% of both the males and females responded "no" when queried about being told they had pre-diabetes. In 63% (males) and 33 %(females) no insurance coverage was documented. While the 12% prevalence for the "lean group" is not alarmingly large, if the present BMI criterion is used, these young adults will be missed in screening, thereby missing the opportunity to further screen/treat/educate for risk of developing T2DM. For this age group, mounting increasing public awareness campaigns addressing this issue among both consumers and providers is warranted.

2367-PO

Comparison of Hypoglycemia Risk and Cost between Oral Antidiabetic Monotherapies in Elderly Patients with Type 2 Diabetes Mellitus

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The objectives of the study were to assess the risks and annual healthcare costs of hypoglycemia associated with oral antidiabetic drug (OAD) monotherapy types in the elderly.

We conducted a retrospective analysis of the IHCIS/Ingenix impact claims database from January 1999 to September 2008. Patients aged ≥65 years with at least two claims for T2DM diagnosis and one claim for an OAD (sulfonylurea (SU), metformin (MET), or thiazolidinedione (TZD)) were followed from the OAD initiation date. Rates of hypoglycemia (ICD-9: 250.8X, 251.0X, 251.1X, or 251.2X) were estimated descriptively for each OAD class. Risk of hypoglycemia associated with each OAD in reference to SU monotherapy was examined using a Cox proportional hazard regression model adjusting for baseline characteristics, antidiabetic treatments and comorbidities. Healthcare costs in the 12 months following the initiation of the OAD were compared descriptively between patients with and without hypoglycemia using Wilcoxon tests.

The sample included 7,620 SU patients, 6,675 MET patients, and 1,940 TZD patients. The rate of hypoglycemia associated with SU, MET, and TZD at 1 year was 2.7%, 1.5%, and 1.3%, respectively. Both MET and TZD were at a lower risk of hypoglycemia than SU (HR=0.63 and 0.49, respectively, p<0.001). Total and diabetes-related healthcare costs were higher in patients with than without hypoglycemia for each OAD (except for total costs in the OAD group; Table).

	SU		MET		TZD	
Annual Healthcare Costs ($, mean±SD)	Hypoglycemia (N=208)	No Hypoglycemia (N=7412)	Hypoglycemia (N=102)	No Hypoglycemia (N=6573)	Hypoglycemia (N=26)	No Hypoglycemia (N=1914)
Total	27,100±36,500	11,460±22,102	23,620±46,090	9880±15,656	18,169±20,268	13,641±26,233
	P<0.001		P<0.001		P=0.183	
Diabetes-related	13,834±25,796	3685±11,710	11,958±42,141	2985±8926	7345±11,604	4216±13,645
	P<0.001		P<0.001		P=0.008	

Among OAD monotherapies, SU poses the highest risk of hypoglycemic events in elderly T2DM patients. Hypoglycemia in all OAD classes is associated with increased healthcare costs.

2368-PO

Cost and Frequency of Blood Glucose Self-Monitoring in Type 2 Diabetes Patients Treated with Insulin in US Managed Care

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Initiation of insulin in type 2 diabetes (T2D) will require more intensive blood glucose self-monitoring (BGM) compared to oral antidiabetics (OAD) alone or other non-insulin therapy, incurring higher costs for BGM. We investigated cost and frequency of BGM in T2D patients initiated onto insulin in order to inform comparative economic evaluations of T2D therapy.

Data from the Pharmetrics claims database was analysed for patients with a first prescription of insulin (= index date) between January 2005 and March 2008, continuous enrolment 12 months before until 12 months after index date, aged ≥ 40, a diagnosis of T2D and who were treated with OAD alone prior to insulin. Frequency and annual cost to payers of BGM (test strips and lancets) was observed for all patients after insulin initiation and sub-groups initiated onto long-acting insulin analogues (LAA: glargine or detemir) only or other insulin regimens. This was compared to frequency and annual cost of BGM with OAD therapy alone prior to insulin initiation.

35,568 patients were identified, average age 61 and 55% male. See table 1 for results.

		Any insulin	LAA only	Regimens other than LAA only
N		35,568	18,610	16,958
Annual BGM cost per patient $ mean (SD)	Prior to insulin - OAD alone	95.85 (204.32)	103.10 (202.05)	87.91 (206.51)
	With insulin	301.28 (510.74)	251.80 (350.81)	355.57 (637.72)
	Cost difference p-value	p<0.001	p<0.001	p<0.001
BGM frequency mean test strips/ patient/day (SD)	Prior to insulin - OAD alone	0.21 (0.45)	0.23 (0.47)	0.18 (0.42)
	With insulin	0.60 (0.90)	0.54 (0.78)	0.66 (1.00)
	Frequency difference p-value	p<0.001	p<0.001	p<0.001

Use of insulin was associated with significantly higher annual BGM cost due to more frequent testing compared to OAD alone, for both LAA only and other insulin regimens.

2369-PO

Cost-Effectiveness of Saxagliptin in Type 2 Diabetes in the United States

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The value of newer therapeutic classes, including DPP-IV inhibitors in the treatment of type 2 diabetes (T2DM) is not well established.

The current analysis evaluated the cost effectiveness of saxagliptin compared with the sulphonylurea, glipizide, as add-on to metformin in T2DM patients, from the US payer perspective.

Data from a 52-week randomized controlled trial comparing saxagliptin and glipizide in combination with metformin was used to estimate the 5-year and 40-year health and economic outcomes. Patient characteristics were based on US demographic data and were comparable to the trial population. Patients were simulated in yearly time increments taking into account the cost and disutility associated with weight gain and hypoglycemic events. The model estimated the direct costs and quality-adjusted life years (QALYs) associated with the incidence of microvascular and macrovascular complications, diabetes-specific mortality, and all-cause mortality associated

For author disclosure information, see page 785.

with the investigated treatment strategies. Economic and clinical outcomes were discounted at a rate of 3%.

The main differences observed between the treatment arms were in their side effect profiles, with patients in the saxagliptin arm experiencing fewer hypoglycemic events, lower risk of severe hypoglycemic events, and a small weight decrease. For the hypothetical cohort of 1000 T2DM patients, treatment with saxagliptin+metformin avoided 1,243 hypoglycemic events in the first 5 years and 1,201 in the 40-year follow-up at an incremental cost of $5,707 and $2,315 per event avoided respectively. In addition, there were 10.69 avoided CV events at 40 years, with an incremental cost of $260,146 per event avoided. Compared with glipizide+metformin, the 5-year QALY gain for saxagliptin+metformin was equal to 0.53 with a cost per QALY of $13,374. The lifetime (40-year) QALY gain for saxagliptin+metformin rises to 2.64 per patient with a cost per QALY of $1,052.

Over a T2DM patient's lifetime, the addition of saxagliptin to metformin is associated with improvement in QALY when considering cost and disutility due to treatment side effects. The cost effectiveness is within an acceptable cost-effectiveness threshold in the US.

2370-PO

WITHDRAWN

2371-PO

WITHDRAWN

2372-PO

WITHDRAWN

2373-PO

Hemoglobin A1c Outcomes in Type 2 Diabetes Mellitus Patients (T2DM) on Combination Oral Antidiabetic Drugs (OADs): Step-Therapy, Loose-Dose and Fixed-Dose Combinations

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The impact of combination OADs (fixed-dose combination [FDC], loose-dose combination [LDC], or monotherapy with subsequent add-on step-therapy [ST]) on hemoglobin A1C (A1C) goal attainment among T2DM patients remains uncertain.

The objective of this study was to evaluate the impact of FDC, LDC, and ST on A1C goal attainment among T2DM patients.

A retrospective claims database analysis was conducted on T2DM patients new to FDC, LDC, or ST, not on insulin, and continuously enrolled in a national health plan from 2006 to 2009. American Diabetes Association (ADA) and American Association of Clinical Endocrinologist/American College of Endocrinology (AACE/ACE) guidelines were used in the assessment of goal attainment. Logistic regression was conducted to examine the impact of the type of combination therapy (FDC, LDC, or ST) on goal attainment, controlling for patient demographics and comorbidities.

A total of 1,926 patients (873 FDC, 341 LDC, 712 ST) were included. FDC patients were younger than patients on ST (mean age: 51.8 vs. 53.2; p=0.002) or LDC (51.8 vs. 54.5; p<0.001). FDC patients had a lower Charlson-Quan score, a weighted score based on the presence of diagnostic codes, than ST patients (1.16 vs. 1.27; p=0.032), but similar to that of LDC patients (1.16 vs. 1.27; p=0.099). A1C goal attainment was assessed in patients who were above goal in the pre-index period (N=1,376 ≥7.0% A1C goal [FDC: 615; LDC: 241; ST: 520]; N=1,586 >6.5% A1C goal [FDC: 701; LDC: 284; ST: 601]). FDC patients had a significantly higher rate of achieving A1C goal of <7.0% (61%) compared with ST (48%; p<0.001) or LDC patients (52%; p=0.015) as well as A1C goal of ≤6.5% compared with ST (45% vs. 35%; p<0.001) or LDC (37%; p=0.021) patients. Logistic regression analysis showed that FDC patients had a significantly higher odds of achieving A1C goal of 7.0% compared with ST patients (ST OR: 0.441; p <0.001; LDC OR: 0.728; p<0.053).

In this analysis of T2DM patients, FDC treatment was associated with better likelihood of A1C goal attainment as defined by current treatment guidelines.

2374-PO

Increased Mortality from Diabetic Ketoacidosis in Greek Ethnic Minorities with Type 2 Diabetes

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Diabetic ketoacidosis (DKA) is a state of absolute or relative insulin deficiency that progresses rapidly and is life-threatening if not properly treated. Hospitalization for DKA is increasing, perhaps due to its rising incidence in patients with type 2 diabetes mellitus (T2DM). This study aimed at elucidating the characteristics of T2DM patients with ketosis-prone diabetes. A 2-years retrospective analysis of adults with T2DM (age 58 +/- 5 years) admitted with DKA was performed.

DKA was diagnosed in T2DM patients with hyperglycemia (glucose >250mg/dL), metabolic acidosis (arterial pH ≤7.3 and/or serum bicarbonate ≤15mEq/L), and presence of ketonuria.

We recorded 106 cases of DKA in 713 insulin-treated patients with T2DM, 75% of who were predominantly Greek ethnic minorities (Albanians or Romanians).

Patients with DKA reported an average of 80% of missed clinical appointments compared to 20% in those without DKA. Readmission with DKA was more common in the Romanian patients in comparison with Albanians (P=0.0001). Patients with T2DM and DKA did not differ significantly in terms of sex, age on admission at the Emergency Room with hyperglycemia and age of diabetes onset than those without DKA. Patients with DKA were more obese (P<0.001), had higher central fat distribution (P=0.04) and had higher blood pressure (P=0.002) than those without DKA. More subjects with DKA had hypertension (P=0.03), cardiovascular (P=0.018) and peripheral vascular disease (P=0.026), peripheral neuropathy (P<0.001) and microvascular complications (P=0.023). Moreover, patients with DKA had longer diabetes duration (P=0.001), worse glycemic control (P<0.001), required more insulin units per day (P<0.001) and used mostly human insulin as antidiabetic treatment (P=0.023); they were mostly on intensified insulin regimen (basal-bolus) (P<0.001). Mortality, which was 2%, occurred only in the ethnic minorities group with T2DM.

DKA is not uncommon in insulin-treated patients with T2DM. Ethnic minorities are more susceptible to developing DKA and have worse prognosis. Poor glycemic control was attributed to inadequate insulin-treatment in most cases, and missed clinic appointments were the main cause of DKA.

2375-PO

Juvenile Diabetes Care Quality in British Columbia: A Population Based Prospective Cohort Study Using Administrative Databases

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Clinical practice guidelines (CPGs) are effective in reducing variation in practice and improving quality of care. The objective of this study was to measure adherence to CPGs among children with type 1 diabetes (T1D) <20 years of age living in British Columbia (BC), Canada.

Care quality was defined as adherence to Canadian Diabetes Association guidelines using the following variables: diabetes-related physician visits, HbA1c measurements, glucagon prescriptions, and screening tests for co-morbidity (eye exams, TSH levels, and urine albumin/creatinine ratios). Each care quality level was assigned an adherence to evidence-based guidelines (ACPG) score ranging from 4=optimal, 3=good, 2=minimal, and 1=poor. Average ACPG is calculated for the six annual cohorts (2001/02 to 2006/7) comprised of incident cases of T1D in children and youth (N=1472), identified by a case-finding definition when applied to a population-based administrative dataset from BC. It was then possible to identify predictors of care quality.

For author disclosure information, see page 785.

Table 1. Characteristics of the four cohorts* (including the ACPG score distribution)&

Cohort	A	B	C	D	E	F
Year of diagnosis	2001/02	2002/03	2003/04	2004/05	2005/06	2006/07
Incident cases (n)	257	250	257	255	211	242
Years of follow up	5	5	5	4	3	2
Average ACPG score	1.94	1.88	1.88	1.95	1.85	1.95
Total person-years	1265	1218	1274	1010	632	483

* data collected between 2001/02 to 2006/07 for patients with type 1 diabetes <20 years or younger living in the province of BC; & ACPG - Adherence to Clinical Practice Guidelines - average score;

In a multivariate regression analysis, years from diagnosis was the strongest (R^2 = 0.063, p<0.001) negative predictor (β = - 0.188) of ACPG score after adjusting for gender, age at diagnosis, local population size and distance from a tertiary care children's hospital.

Indicators of process derived from population-based administrative datasets provide valid and useful information for assessing adherence to evidence-based clinical practice guidelines and to further assess the impact of interventions.

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2376-PO

Managing Diabetes in a Large Academic Center: Is It Safe, Sustainable?

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Improved glucose control has been shown to reduce morbidity, mortality and shorten hospital stay but is difficult to achieve safely and consistently. Objectives 1) Improved glycemic control 2) Reduced in hypoglycemia, 3) Standardization of care of patients with diabetes (DM) across the hospital system. The patient population included individuals with primary or secondary diagnosis for DM, excluding pregnancy, organ transplantation, TPN, and age <18. The data were pooled from inpatient stays at the OSUMC over the following time periods: Jan-Feb 2005 (baseline), Jan-Feb 2006 (initiation of education, modification of pharmacy site and ordering screens), Jan-Feb 2007 (3 months post-initiation of nurse-managed insulin drip guideline and use of carbohydrate counting), Jan-Feb 2008-2010 (long-term follow up).

Results: There were approximately 2000 encounters per time period, data was taken from Hospital day 2.

	Median BG (mg/dl)	%<70mg/dl	%EffectiveTx	%SSI	% Drip
2005	161	3.4	8	33	4
2006	155	3.2	11	51	4
2007	152	3.8	26	58	10
2008	154	3.4	44	54	12
2009	150	3	40	57	10
2010	155	3	37	26	11

The use of subcutaneous and intravenous insulin increased significantly. There was less hypoglycemia with insulin drips vs. subcutaneous insulin, insulin:carbohydrate ratios vs. sliding scale insulin.

In summary, patient care and practitioner ordering patterns were improved. Blood glucose targets were attained consistently by hospital day 2 with no significant change in the rates of hypoglycemia. Care variability, with regards to glucose control, hypoglycemia, ordering patterns for insulin and use of the diabetes consultation service was identified and continues to be addressed across the system. In conclusion, the results of the project demonstrate that improvement in glycemic control can be done safely and effectively in a large academic center. However, a commitment from all levels of leadership and staff, constant surveillance and feedback, education and retraining is necessary to maintain safe, effective and sustainable glucose control.

2377-PO

Overweight and Obesity in Those Age 3-17 Years Old: Implications for Diabetes Prevention

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We evaluated initial BMI data from a longitudinal pediatric cohort study (to run from 1/1/07 to 12/31/12) based on electronic medical record (EMR) data of children (3-11 yr) and adolescents (12-17 yr) from 3 large US health plans. Current data are available on 244,523 subjects through 12/31/09. We collected longitudinal and cross-sectional data from clinic records including gender, age, race, height, and weight. Body mass index (BMI) percentiles were calculated using height, weight, gender, and age, based on the CDC-established reference growth charts. We report here BMI percentile, based on single measures.

The cohort consists of 244,523 subjects (58.3% 3 -11 years of age, 41.7% 12-17 years, and 50.1% female). We report the proportions of children and adolescents having initial clinical measurements that meet or exceed the 85th BMI percentile of BMI at time of entry into the cohort (Table).

Pediatric Cohort, US, 2007-2009: Baseline BMI percentile according to age.

N=244,523	Baseline age (years)				
	3-5	6-11	12-14	15-17	All
Baseline BMI≥ 85th percentile (%)	22.6	31.7	33.2	31.1	29.8

Measures collected at the initial clinical visit indicate high levels of overweight in all age categories, including age 3-5 years, confirming that effective public health and clinical strategies to mitigate overweight and prevent type 2 diabetes need to reach children below age 6 and possibly below age 3. Further analysis will provide additional insight on persistence of elevated BMI percentile over time, and elucidate the impact of BMI on glucose metabolism, BP, and other cardiovascular risk factors.

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2378-PO

WITHDRAWN

2379-PO

Satisfaction with Treatment and Factors Associated with Longer Length of Hospital Stay amongst Diabetes In-Patients

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Hospitalized patients with diabetes stay longer as inpatients regardless of the cause of admission and are often reported as being unhappy with the level of care they receive. We prospectively studied factors associated with longer length of stay (LOS) and evaluated patients' satisfaction using a validated Diabetes In-patient Treatment Satisfaction Questionnaire (DTSQ-IP) in our in-patients. Data are means ± standard deviations. Eighty five patients (58.8% male, 85.7% Type 2 DM) participated with mean age 65.7±15.4 years, BMI 34.1±13.6 kg/m^2, diabetes duration 9.9±8.7 years and Hba1c 7.9±2.4%. The majority of patients were attending hospital outpatient care (85.1%). The frequency of capillary blood glucose (CBG) was 4.1±1.4 per day. Although, 37.2% were insulin treated, almost two thirds (62.5%) had their insulin administered by a nurse i.e. loss of independence. Most patients (68.8%) had at least one episode of hyperglycaemia (BM>10) and 18.2% had at least one episode of hypoglycaemia. Only 22.1% were seen on consultation and 18.2% were seen by a diabetes nurse specialist (DNS). Mean LOS was 11.7±8.8 days. Mean DTSQ-IP score was 85.3±13.0 (maximum 102) indicating a high level of satisfaction. Age (r=0.33, p=0.001) and CBG frequency (r=0.25, p=0.031) positively and HbA1c (r=-0.25. p=0.015) negatively correlated with longer LOS. There was no correlation between LOS and DTSQ-IP (r=-0.057, p=0.612). There was a negative correlation between CBG frequency and modified DTSQ-IP score (r=-0.523, p=0.006). Satisfaction with current treatment was greater amongst patients visited by DNS compared to those who were not (p=0.018). Patients seen on consultation were more likely to have a LOS < 1 week compared to those who were not (64.7% vs. 35.3%, p= 0.039). Presence of macrovascular complications (p=0.03), higher age (p=0.01), higher CBG frequency (p=0.03) and lower HbA1c (p=0.03) were associated with LOS >7 days. In summary, older patients with complications had longer LOS and lack of specialist involvement also contributed to longer LOS. Addressing this issue might reduce the length of hospital stay for diabetes patients.

2380-PO

The Ability of a Simple Diabetes Risk Test To Identify Individuals for Diabetes Prevention Intervention

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In diabetes prevention translation, simple tools to identify those at risk for diabetes prevention services are lacking. The National Diabetes Education Program (NDEP) risk test was developed to identify those at risk for developing diabetes who should receive further evaluation. To our knowledge its use as a tool to identify persons eligible for diabetes prevention services has not been examined. The objective of this investigation was to assess the ability of the NDEP risk test as compared to a simple Body Mass Index (BMI) cut-point to identify individuals with pre-diabetes and/or the metabolic syndrome to take part in a study to evaluate the Group Lifestyle Balance (GLB) program, an adaptation of the Diabetes Prevention Program lifestyle intervention, in a worksite setting. Non-diabetic adults with BMI ≥24kg/m^2 took part in screening for the study, with the following measures completed: height, weight, waist circumference, blood pressure, fasting glucose and lipids, and A1C. Screened participants also completed a paper NDEP risk test. Intervention eligibility criteria included: pre-diabetes (fasting glucose of 100-125mg/dl and/or A1C of 5.7%-6.4%), and/or the metabolic syndrome (NCEP ATP3 criteria or hyperlipidemia and 1 component of the metabolic syndrome). Of those screened (N=147), 100 subjects met the eligibility criteria. Mean participant age was 49 years, mean BMI was 32.4 kg/m^2 and 60% were female. Results of sensitivity and specificity analyses are shown in the table.

	NDEP Risk Score			BMI ≥ 27 kg/m^2		
	Sensitivity (%)	Specificity (%)	Predictive Value + (%)	Sensitivity (%)	Specificity (%)	Predictive Value + (%)
All Eligible	88	29	72	86	32	72
Pre-diabetes	87	22	50	82	22	49
Metabolic Syndrome	87	21	45	87	25	46

NDEP Risk Score

Our results indicate that the NDEP risk score and a BMI cutoff of 27kg/m^2 have similar ability to identify individuals who meet the definition of pre-diabetes or metabolic syndrome, although both identify a large number of participants who do not meet eligibility criteria.

2381-PO

WITHDRAWN

2382-PO

WITHDRAWN

2383-PO

The New Paradigm in Glucose Control: Computer Time Has Come

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Inability to meet mandated targets in glucose, HgA1c without more hypoglycemia, body weight and mortality suggest limitations in the current Rx paradigm.Trials like ACCORD, have proven the point: we need a new paradigm shift .If what we need is weekly frequent prescription change, like DCCT, daily companion for adjusting metabolic life prediction, averting hypoglycemia we need computing power to test in real life practice .This abstract describes experience with computer diabetes therapy.

Methods: Each component tested in N-of 1 trial format where patient is own control for efficacy, safety, privacy, cost effectiveness and value. The original 87 Patients instructed, did SMBG 8 time's weekly, made changes by computer instructions based on modified ADA/ AACE algorithms with outcome at baseline and quarterly. The recent internet based model used a memory flash disc less than a finger in size, could predict blood glucose values up to 48 hours based on today therapy, thus averting hypoglycemic risk: it is patient friendly, 24hours/7days ready continuous diabetes provider decision support system.

Results: Of the 60 compliant patients non-adherence was seen in 10%. 97.2% improved. 2.7% did not despite good Compliance and Adherence needing insulin pump. Improved measures included in table 1.

Means average	FBS	2h PP	HgA1c%	Insulin dose%
Baseline	167	194	9.7	X
On computer	140	152	7.4	-22%
Off computer	160	189	8.9	+25%

In non users of the system HgA1c increased 0.4% with absolute difference of HgA1c:2.7%.

Discussion: DM chronic disease with huge data and numbers (at least 35 numbers per week) challenging every provider. The only reasonable manner to handle is to use computing power to treat effectively, since computing has been used to solve the most difficult challenges from cell biology to space exploration! Using computer HgA1C was %2.7 better in users Vs non users.

Conclusion: Computer diabetes therapy improves all parameters of metabolic control with less staff, without hypoglycemia, weight gain, and less insulin dose. As a result, this paradigm shift deserves new major trial based on this technology described without delay. Otherwise we might find ourselves again asking in 2020: Why have not we done it yet, who will we blame?

2384-PO

The Role of Illness Perceptions in Achieving Diabetes Outcomes

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Over the last decade there has been an increased focus on improving diabetes management. There has also been an increased emphasis on paying providers for optimal diabetes control. The goal of this study was to evaluate the role of patient beliefs about their diabetes on control of their diabetes and other risk factors.

We identified all type 2 diabetes patients from two practices in south central Minnesota (n=1,427). Patient laboratory values were available from a diabetes registry. All patients were sent a survey to assess their beliefs about their diabetes (using the Brief Illness Perception Questionnaire), their activation level (using the Patient Activation Measure), and their assessment of the diabetes care delivery (using the PACIC). Multivariable regression analyses was used to assess the role of illness perceptions on diabetes control (hemoglobin A1c<7%) and control of other common risk factors: lipids (LDL<100) and blood pressure (BP<130/80). In addition, we evaluated the role of illness beliefs on control of all three measures simultaneously.

Patients (n = 536) had diabetes for an average of 9.3 years with a mean HgA1C of 7.1 (SD 1.4). Approximately, 56.2% had a hemoglobin A1c>7%, 66.5% had a LDL>100 and 51.7% had BP>130/80. 22% had all three measures controlled. Duration of diagnosis and increasing age were associated with a lower likelihood of A1c control ($p<0.05$). Greater personal control of diabetes was associated with better control of both A1c, LDL, and diastolic blood pressure ($p<0.05$). A stronger emotional response was associated with worse control for systolic blood pressure. A greater number of consequences and concern for diabetes were associated with a lower likelihood of achieving control for all three symptoms ($p<0.05$).

A better understanding of illness perceptions may help enable better control of diabetes. To improve patient engagement and outcomes, routine assessment of illness perceptions may guide clinical care and education.

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2385-PO

WITHDRAWN

For author disclosure information, see page 785.

2386-PO

Type 1 Diabetes Average Glycemic Control in the Public Health System of a Developing Country. The First Nationwide Survey in Type 1 Diabetes in Brazil

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Type 1 diabetes (T1D) is associated with increased mortality and morbidity due to its chronic complications. Tight glycemic control has an established importance in the prevention of these complications. However, many factors can influence glycemic control. The aim of this study was to determine the factors that can interfere on glycemic control in a nationwide survey of T1D conducted between January 2009 and December 2010 in 28 public clinics from 23 Brazilian cities. Medical records from 3591 patients (56.9% females, 56.7% Caucasians), aged 21.0 ± 10.4 years, age at diagnosis of 11.7±7.9 years, duration of T1D of 9 ± 6.9 years were analyzed. The sample was representative of Brazil's population density. Overall 3344 (93.4%) patients had HbA1c measurements Five analytic methods were identified, four certified by the National Certified Standardization Program. Because each method had 3 to 5 different reference values a random sample of 1222 patients participants of this nationwide survey stratified by age, gender, duration of diabetes had A1c measured by the same method (HPLC;Variant Turbo-Biorad). One-way ANOVA, Mantel-Haenszel test and multivariate analysis with thigh glycemic control (Yes/No) as dependent variable and other variables of interest as independent variables were performed. The mean A1c levels were 9.6 ± 2.4% (estimated mean blood glucose of 227.7 ± 68.1 mg/dL). Overall, 14.6% of the studied population presented tight glycemic control. The target of A1c established by age-group as tight glycemic control was obtained by 55.3% of toddlers, 23.6% of schoolars, 12.7% of adolescents and 9.6% of adults (p=0.0001). A higher A1c was observed in patients from low socioeconomic class and in the Northeast region (p<0.05).

We concluded that low socioeconomic level and age are related to metabolic control. In addition, this first nationwide survey suggests that is necessary to standardize A1c in the country to overcome the barriers for evaluating metabolic control among TIDs in Brazil.

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2387-PO

Under-Diagnosis and Suboptimal Management of Adult Diabetes Mellitus in the U.S.: An Analysis of Electronic Medical Records

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Objectives: To assess in primary care practices in the U.S.: 1) the extent of undiagnosed diabetes; and 2) the clinical management of patients with known diabetes, according to frequencies of meeting selected indicators of diabetes care quality.

Research Design and Methods: Retrospective descriptive analysis of clinical and laboratory data derived from a nationally representative database of electronic medical records (GE Centricity) of patients attending primary care practices in the U.S. in 2008/09.

Results: Records from 10,430,056 non-diabetic patients were assessed for fasting and random glucose values diagnostic of diabetes. At least 2 abnormal values were present in 0.39% (n = 40,359) and of the remaining patients, another 0.23% (n = 23, 261) had at least one elevated HbA1c recorded.

Of 622,260 patients with known diabetes for at least 15 months, only 59% had HbA1c testing in that interval; 34% were at goal (<7%). BMI was recorded in 57%; blood pressure was recorded in 88% with 68% <145/85 mmHg; 33% had urine checked for micro-albuminuria; 69% had a serum creatinine recorded; 86% were appropriately treated with ACE or ARBs; 60% had total cholesterol recorded, and 45% were ≤ 5 mmol/L. Regional differences in the prevalence of undiagnosed diabetes and in satisfaction of indicators of care quality were noted.

Conclusions: It is feasible to apply a simple algorithm to a nationwide database of electronic medical records to identify patients with potentially undiagnosed diabetes.

Furthermore, our analysis of indicators of quality of care in patients with known diabetes suggests that a wide gap exists between recommended and actual practice.

Supported by: GE HealthCare

2388-PO

WITHDRAWN

2389-PO

Obesity Prevalence Declines among High School Students

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Obesity in children and adolescents developed into a major epidemic during the last decade but now there are reports that obesity rates are beginning to stabilize. The HEALTHY study showed a significant decline in obesity rates even in control schools, suggesting that changes in indices of overweight may constitute a secular trend rather than result from specific interventions.

The purpose of this study was to determine whether there were differences in the prevalence of obesity and other obesity measures between two cohorts of students nine years apart. The study took place in a California public high school. During the Fall semester of 2001, 439 students (147 male, 292 female) participated in a survey that included measurements of height, weight and % body fat (Tanita® body composition analyzer). During the Fall semester of 2010, 189 students (99 male, 90 female) enrolled in all periods of two required classes were measured in an identical manner. Students in both study years ranged in age from 14-18 with a mean of 15.7 and 15.6 for males and females, respectively, in 2001, and of 15.6 and 15.3, respectively, in 2010.

The table shows rates of overweight/obesity (BMI ≥85th percentile for age and sex), mean BMI, and mean % body fat by sex in 2001 versus 2010.

	Sex	2001	2010	Analysis	p-value
Overweight/obese	M	58 (39.5)	27 (27.3)	CMH*=5.60	0.018
	F	101 (34.6)	24 (26.7)		
BMI	M	24.0±4.8	22.3±4.8	F**=6.95	0.009
	F	23.7±5.3	22.8±4.3		
% Body Fat	M	18.3±8.5	15.8±8.4	F**=4.20	0.041
	F	29.1±8.1	28.8±8.6		

Results are shown as n (%) or mean±s.d.
*CMH=Cochran-Mantel-Haenszel statistic, controlling for sex
**F= General Linear Regression, controlling for age and sex

Students in 2010 were significantly less likely to be overweight or obese than were those in 2001 (OR=0.865, 95%CI=0.771-0.970) and had a significantly lower mean BMI and % body fat.

Concern escalated throughout the public health and healthcare provider sectors regarding obesity in youth between the time periods sampled, leading to increased awareness of obesity as a major health issue. In response, schools instituted some overall improvement in foods and beverages available on campus. Data from this survey showing adolescent obesity on the decline are very encouraging.

2390-PO

A Case Report of New-Onset Type 1 Diabetes Mellitus with Diabetic Ketoacidosis, Deep Vein Thrombosis and Pulmonary Embolism—A Rare Presentation

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We report a case of a 14 year old caucasian female who presented with a 3 day history of right leg swelling, pain and difficulty in ambulation. She had no respiratory compromise and was maintaining saturations of 97-98% on room air. There was no appreciable weight loss, polyuria, polydipsia and polyphagia. She was started on oral contraceptives (OCP) drospirenone 3 mg/ethinyl estradiol 20 mcg(YAZ®) about 2 months ago. There was no family history of thrombotic disease, diabetes or any other endocrine disorder. Physical exam showed moderate dehydration and physical signs of deep vein thrombosis(DVT). Doppler ultrasound of lower extremity showed occlusive DVT within the right popliteal vein extending to the external iliac vein. Angiographic CT scan of chest indicated left pulmonary embolus. Laboratory

For author disclosure information, see page 785.

investigations showed elevated PT, INR, PTT, D dimers, fibrinogen, low antithrombin 3, negative serum HCG, elevated white blood count and hematocrit. Basic metabolic profile showed a sodium of 130 mEq/L, serum bicarbonate of 10 mEq/L blood glucose of 280 mg/dl with elevated anion gap of 17 mEq/L. Urinalysis indicated 3+ ketones, 3+ glucose with specific gravity of 1.04. She had elevated insulin antibodies(Ab), elevated islet cell autoAb:ICA-512/IA-2 Auto Ab, normal glutamic acid decarboxylase auto-Ab and Hemoglobin A1c of 11.9%. She had normal insulin C-peptide, thyroid hormones and negative celiac screen. Factor V Leiden, prothrombin gene(factor II) variant and 20210G>A mutation was negative. She was treated with intravenous fluids, insulin and heparin. In summary, the profound hypovolemic state due to diabetic ketoacidosis(DKA) and hypercoagulability risk secondary to the usage of OCP as well as type 1 diabetes mellitus with DKA caused DVT and pulmonary embolus. To the best of our knowledge, this is the first reported case of new-onset type 1 diabetes mellitus presenting with this combination of DKA, DVT and pulmonary embolism.

2391-PO

Camel Milk, Adjunct to Insulin Therapy Improves Glycemic Control and Lowers Insulin Requirement without Risk of Hypoglycemia in Patients with Type 1 Diabetes: 2 Years Randomized Controlled Trial

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Hypoglycemic effect of camel milk supplementation in experimental rat model and significant reduction in doses of insulin in type-1 diabetic patients have been observed in our previous studies. This long-term study was undertaken to assess the efficacy, safety and acceptability of camel milk as an adjunct to insulin therapy in type-1 diabetics. In this two year randomized clinical parallel design study, 24 type-1 diabetics were enrolled and divided in two groups. Group-I (n=12) received usual care i.e. diet, exercise and insulin and group-II (n=12) received 500ml camel milk in addition to usual care. Insulin requirement was titrated weekly by blood glucose estimation. Results were analysed using ANOVA. In camel milk group, there was significant decrease in mean blood glucose (118.58±19 to 93.16±17.06 mg/dl, $p<0.001$), HbA_1c levels (7.81±1.39 to 5.44±0.81%, $p<0.05$) and insulin doses (32.50±9.99 to 17.50±12.09u/day, $p<0.05$). Out of 12 subjects receiving camel milk, insulin requirement in 3 subjects reduced to zero. Non-significant changes in C-peptide, plasma insulin and anti insulin antibodies were observed in both the groups. Camel milk is safe and efficacious in improving long-term glycemic control with a significant reduction in the doses of insulin in type-1 diabetic patients.

2392-PO

Comparison of Insulin Detemir in a Twice Daily Insulin Regimen Versus a Three Times Daily Insulin Regimen in Children with Type 1 Diabetes: A Randomized Controlled Trial

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Children with type 1 diabetes (DM1) require multiple daily injections of insulin and often use three times daily (TID) injections with intermediate acting insulin at breakfast and bed-time, and rapid acting insulin at breakfast and supper. In families that express a preference for fewer injections, substituting the intermediate acting insulin at bed-time with a long acting insulin analogue (LAIA) at supper in a twice daily (BID) injection regimen may result in a better quality of life while decreasing the risk of nocturnal hypoglycemia. The objective of this study was to compare glycemic control in children with DM1 using a BID regimen with a LAIA at supper with children using a standard TID regimen over a 6 month period.

This was a randomized controlled trial (intervention was a BID regimen with insulin detemir at supper, control group remained on a TID regimen). The main outcome measure was HA1c at 0, 3 and 6 months. Secondary outcomes were frequency of adverse events (hypoglycemia, diabetic ketoacidosis, weight gain) and scores on the Diabetes Quality of Life Measure for Youths (DQOLY).

18 subjects were enrolled (10 control, 8 intervention). Age at diagnosis of DM1, mean(SD), was 6.31(2.91) years for control and 7.76(3.22) years for intervention. Mean duration of DM1 was 5.96(4.95) years for control and 3.76(3.37) years for intervention. There were no significant differences in the mean HA1c between control and intervention at 0 months [8.48(0.86) vs 8.57(1.13)], 3 months [8.47(0.50) vs 7.99(0.61)], or 6 months [8.42(0.63) vs 8.30(0.76)]. No significant differences were found between the groups for adverse events or DQOLY.

In conclusion, simplifying to BID insulin regimens incorporating LAIA is possible with no increase in adverse events and comparable HA1c compared to standard TID regimens used in children. Although no significant improvements were seen in DQOLY and nocturnal hypoglycemia, it is important that HA1c remained stable, and suggests that this regimen is a viable option for families where a more simplified insulin regimen would be beneficial and compliance may be improved.

2393-PO

Continuous Subcutaneous Insulin Infusion in Prepubertal Children

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To evaluate if despite unique difficulties in the management of children with type 1 diabetes (T1D) recognized under the age of 5 continuous subcutaneous insulin infusion (CSII) can assist in achievement of similar goals of treatment in this group as in the older subjects.

There were included into the study prepubertal children with T1D treated with CSII for up to 6 years. I group: 76 children, with mean age at pump initiation 3.1±1.1ys (range: 0.9-4.9) Mean duration of diabetes at initiation of CSII was 1.5±0.8 ys (range: 0-3.2). II group: 65 children, with mean age at pump initiation 8.3±1.4ys (range: 5.3-10.7). Mean duration of diabetes at initiation of CSII 1.7±1.3 ys (range: 0-5.7). Into the III group there were included 50 children with the mean age at pump initiation 1.6±0.4ys (range: 0.8-2), with mean duration of diabetes at starting CSII 0.1±0.2 ys (range 0-0.5) who received pump therapy for at least 1 yr (from 1 to 4 ys). Data was collected retrospectively: HbA1c, BMI-sds, diabetic ketoacidosis (DKA), severe hypoglycaemia (SH), and daily insulin dose (TDD).

In the I group HbA1c was <7.5% during the follow-up p=0.419. In the II group HbA1c was <7.5% throughout 5 years and increased to 8% in the 6^{th} year $p<0.0001$. In the III group HbA1c was <7.4% during the follow-up, p=0.184. In the I group TDD increased from 0.58±0.25 IU/kg/day to 0.8±1.18 IU/kg/d, $p<0.0001$; in the II group from 0.56±0.27 IU/kg/d to 0.94±1.18 IU/kg/day, $p<0.0001$; in the III group from 0.66±0.19 to 0.77±0.15 IU/kg/d, p=0.008. There was no statisticaly significantly changes in BMIsds during the study period. There were 1.5 episodes of SH per 100 patient-years in the I group, and 2.1 episodes in the II group. There were 1.6 episodes of DKA per 100 patient-years in the I group and 1.4 episodes in the II group. In the III group there were 2 episodes of DKA and 4 episodes of SH.

This study, along with previous reports confirms that the youngest children with T1D similarly to older colleagues can achieve adequate glycemic control without increased risk of hypoglycaemic events. Insulin pump therapy should be presented as a choice of diabetes treatment for all prepubertal children, especially in the youngest age.

2394-PO

Glycaemic Variability in Diabetics Children and Adolescents

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Glycaemic variability refers to the circadian variation of glycaemic values of a patient due to several causes, as rebound after hypoglycemia, down phenomenon and postprandial hyperglycemic spikes.

Recently, epidemiological and experimental evidences suggest that glucose fluctuations may play a pathogenic role in diabetic complications (especially cardiovascular), together with HbA1c levels and genetic predisposition. However, there is no definitive demonstration from randomized clinical trials.

The aim of our study was to evaluate the parameters of glycaemic variability in a group of children/adolescents with type 1 diabetes subject to multiple daily insulin therapy. We also tested a possible correlation with anamnestic and clinical parameters and the degree of metabolic control to verify whether glycemic variability constitutes an added value compared to simple evaluation of HbA1c.

The glycemic variability indexes (average blood glucose, SD and Kovatchev's Indexes HBGI/LBGI/ADRR) were calculated on 65 patients (median age 12,96) on the basis of SMBG recorded in the last month of home assessment. The sample was divided into 2 groups by the degree of metabolic control and then changes in variability's parameters were calculated (t Student test).

The mean of average blood sugar levels falls within limits of acceptability according to Hirsch; however the risk class of Kovatchev falls under moderate hypoglycemic (LBGI) and global (ADRR) risk, and high risk for hyperglycemic (HBGI).

The degree of glycaemic control significantly correlates with: Total daily and slow insulin, mean glucose values, HBGI and ADRR.

For author disclosure information, see page 785.

Our study revealed a statistically meaningful difference for mean blood glucose (p 0.01), HBGI (p 0.009) and ADRR (p 0.025) but not for LBGI, in patients with better metabolic control.

In summary, metabolic instability of diabetes mellitus in children has been confimed, particularly in adolescents.

As Hypoglycemic risk is also evident for inadequate value of metabolic control, we believe that assessing glycemic variability parameters, in addition to HbA1c, is an useful adjunct in the management of diabetic children and adolescents and could lead to better management of therapeutics changes.

2395-PO

Lessons from Celiac Disease Screening in Newly Diagnosed Children with Type 1 Diabetes

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Objective: assess rate of celiac screen seropositivity, presentation, and weight regain following diagnosis (Dx) of type 1 diabetes (T1D) in children and adolescents.

Methods: Chart review of pediatric cases, all admitted to Rady Children's Hospital at diagnosis of T1D, was IRB-approved for the study of weight regain patterns post-Dx. All received insulin glargine at dinner. Universal screening for celiac disease began for all newly diagnosed T1D cases in 2007, using IgA anti tissue transglutaminase (TTG), and total IgA (to exclude deficiency). We compared weight and BMI % change from Dx till 10 weeks post-Dx, a time weight regain reaches a plateau (1).

Results: 143 subjects with T1D had celiac screen in 2007-2008. Eight subjects (4 males, 4 female, 5 Caucasian, 3 Hispanic) with mean age at Dx of 9.6 years, had elevated TTG titers (5.6%). Of those, 3 children were symptomatic with abdominal complaints, and 4 had biopsy confirmation of celiac. All 4 with no biopsy done were asymptomatic. One moved away, the others were watched clinically, 2 having low TTG titers. TTG titers did not predict symptoms. Weight loss at Dx of T1D was not considered as symptomatic for celiac disease. Compared with our prior data (1) on weight regain following Dx of T1D in 136 subjects, of similar age and ethnic distribution (64% Caucasian, 25% Hispanic) to the current cohort, mean weight regain post-Dx was similar in both groups. BMI Z score at Dx was -0.07 vs -0.28 in the celiac group vs controls, and rate of DKA was 25% vs 27%, respectively. At 15-41 and 42-70 days post-Dx, % BMI changes were 11.7% and 13.1% in celiac cases versus 11.5% and 13.6% in T1D controls, respectively.

Conclusion: BMI-Z score at Dx of T1D and weight regain soon after Dx of T1D may not be good indicators of celiac disease. Screening and full celiac panel testing when having an abnormal screen can help diagnose children early, as many are asymptomatic 1. Rapid weight gain in children soon after diagnosis of type 1 diabetes: is there room for concern? Newfield RS, Cohen D, Capparelli EV, Shragg P. Pediatr Diabetes. 2009 Aug;10(5):310-5

2396-PO

The Phenomenon of Pump Therapy in Reduction Daily Insulin Requirement. The Results of Parallel Study on Multiply Daily Injection vs Continuous Subcutaneous Insulin Infusion

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Continuous subcutaneous insulin infusion (CSII) is an alternative to multiply daily injection (MDI) method of insulin delivering in type 1 diabetes patients. In numerous studies have been proofed that CSII reduced the risk of sever hypoglycemia, improve of metabolic control and quality of life in short and longer time of observations. There are still lack of evidences on the efficiency of this method in the term of individual insulin requirement. The aim of study was to asses the insulin requirement in total and basal daily insulin dose in CSII comparing to MDI method of insulin delivering. The parallel, day-to-day study enrolled 41 pediatrics patients (med. age 9,1 1,3 – 17,9 ys; diabetes duration med.0,5 from 0,01 to 12,7ys, HbA1c med 7,3 from 6,0 to 12,8%); 15 patients used long action analogues, 23 NPH insulin; 31 short acting analogues and 10 regular insulin. It was conduced in clinic where the same diet, meals' pattern, medical health care provider and environment were kept. The median total daily insulin requirement (IU/kg/day) in CSII method was 16,9 from 1,6 to 68 IU/kg/d vs MDI med. 19 from 3 to 79 IU/kg/d p<0.005 respectively. The insulin requirement was reduced by 28% in basal and total daily insulin dose. The glycemia 8-point profile was better when CSII method was introduced (med. 120 from 77 to 221 vs MDI 130 from 86 to 245 mg/dl;p=0,11). Analysis, where type of basal insulin: analogue ALi, NPH were considered, showed reduction by 33% in MDI NPH group comparing to 28% in MDI Ali (levemir+glargine) without deterioration in glucose 8-point profile. The highest reduction by 45% in total daily insulin requirement (med.0,45 from 0,16 to 0,81vs MDI med. 0,75 from 0,33 to 1,55 IU/kg/d., p=0,005 respectively) was in the youngest group of patients aged 0-7ys old with lower glycemia profile med. 129 vs 139 mg/dl p=0,4. CSII method has an impact on reduction in total and basal daily insulin requirement. In the algorithm of insulin programming in CSII, the reduction of TDD -MDI by 30% should be considered, particularly in preschoolers and in patients used NPH insulin.

2397-PO

Two Episodes of Cerebral Edema in a Newly Diagnosed Diabetic

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Cerebral edema is a leading cause of death in childhood caused by Type 1 Diabetes Mellitus (T1DM). It is thought to occur in 0.3-1% of episodes of Diabetic Ketoacidosis (DKA). Known risk factors include new diagnosis, age < 5 years, severe acidosis, elevated urea, treatment with bicarbonate, rapid changes in serum sodium and osmolality and the use of hypotonic solutions for rehydration.

A 7-year-old female presented to the A&E department with a weeklong history of polyuria and polydipsia. She was noted to be confused (Glasgow Coma Scale 14/15). Her clinical examination revealed dehydration. A diagnosis of T1DM was made and she was found to be in DKA with blood glucose of 28.2 nmol/l, blood ketones of 3.3mmol/l and a venous pH of 7.12. Her urea was elevated at 9.2mmol/l. She was rehydrated according to protocol. As this finished and prior to commencing insulin therapy her level of consciousness suddenly changed (GCS 7/15). She was immediately intubated, ventilated and treated with mannitol. CT confirmed cerebral edema. Intravenous insulin was commenced and over the following 24 hours all of her parameters normalized gradually. She was extubated 24 hours after presentation and commenced subcutaneous insulin at that time. Her GCS returned to normal and she was neurologically back to baseline.

24 hours later, she had a sudden drop in her level of consciousness again (GCS 9/15). She immediately responded to a dose of mannitol and her GCS normalized within 30 minutes. MRI Brain revealed foci of acute ischemia in multiple areas particularly the base of the cerebral hemispheres, suggestive of pressure effect related to the episodes of cerebral edema.16 months later she is neurologically normal apart from mild impairment in working memory and attention.

This case report describes a newly diagnosed diabetic child with 2 episodes of symptomatic cerebral edema, the second occurring after DKA had resolved and following a 24-hour period of lucidity. Our patient had 2 known risk factors for cerebral edema (new diagnosis and elevated urea at presentation) but was managed according to best practice international guidelines and despite this had a recurrence of cerebral edema 48 hours after her initial presentation.

PREGNANCY

2398-PO

50/50 Insulin Mix 3x Per Day Simplifies Insulin Regimen in GDM

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Gestational diabetes mellitus (GDM) often requires the use of insulin to achieve normoglycemia, however basal/bolus dosing NPH and rapid insulin in 6 separate injections is cumbersome for insulin-naive patients. A more convenient regimen may improve adherence. We undertook this trial to compare a 50/50 mixture of NPH/lispro delivered as 3 pre-meal injections, with NPH and lispro delivered as 6 distinct injections.

Forty women with GDM unable to achieve a fasting glucose <90mg/dL and a 1-hour postprandial <120mg/dL after at least one week of lifestyle modification were randomized to either 50/50 mix given as 3 pre-meal injections daily or NPH insulin injected every 8 hours and lispro administered before meals (6 injections/day). Both groups received care at the Santa Barbara Prenatal Endocrine Clinic, which includes education on GDM diet, lifestyle and self-monitoring blood glucose before and 1-hour after meals. Outcome measures included fasting glucose and A1C.

The two groups had comparable initial A1C, BMI and gravidity and delivered at similar gestational ages (p>0.05 for each) but the 50/50 mix group was younger (29.6 years) than the standard group (33.6 years, p<0.016). Eighty-six percent were of Mexican descent. The table below demonstrates that outcome measures were similar in both groups. Two women in the 50/50 mix group and 1 in the standard group dropped out of the study.

Outcome Measure	50/50 Mix 3x per Day	NPH and Lispro 6x per Day	p-value
Fasting Glucose (mg/dL)	86±7	82±8	0.120
Mean A1C	5.5 ±0.3	5.6 ±0.3	0.973
Large for Gestational Age	1(5.6%)	3(15.8%)	0.604
Birth Weight (g)	3178 ±501	3375 ±419	0.203
Primary Cesarean Section	2(16.7%)	2(14.3%)	1.000
Daily Insulin Dose (units/kg)	1.0±0.3	1.2 ±0.5	0.250
Weight Gain (kg/week)	0.2 ±0.3	0.3 ±0.2	0.224

Results are mean±SD or n(%).

Insulin 50/50 mix injected 3x per day is a safe and reasonable alternative to 5 or more injections of NPH and rapid-acting insulin. Contrary to the belief that more injections confer better control, 50/50 mix resulted in equivalent glycemia and outcome measures. Simplifying the insulin regimen may improve adherence and obviate the use of oral agents for the treatment of gestational diabetes.

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2399-PO

A Retrospective Study To Assess the Prevalence of Thyroid Dysfunction in Pregnancies Complicated by Pregestational Diabetes

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Maternal hypothyroidism has been implicated in adverse pregnancy outcomes. Hypothyroidism affects 1 in 1600-2000 deliveries. Subclinical hypothyroidism (SH) has been reported in 2-3% of pregnancies. Data on the prevalence of thyroid dysfunction in diabetics is lacking. Thyroid profiles of pregnant patients with Pregestational Diabetes (PDM) were obtained to assess the prevalence of thyroid dysfunction.

We reviewed 500 charts of patients aged 18-50 years old all of whom had PDM and were followed by EVMS Maternal Fetal Medicine from 2007-2009. We excluded 276 patients due to incomplete data. Data abstracted included: demographics, DM or thyroid treatment history and pregnancy outcome data. Trimester specific values for the measurement of TSH in the 1st and 2nd trimester of pregnancy were used. Data analysis was done with Chi square and Fisher exact and Student T test; $P < 0.05$ was significant.

No differences were found when comparing patients with thyroid dysfunction to those without in terms of age, BMI, presence of comorbidities, HbA1c or age at DM diagnosis. Of 224 studied, 20% (n=45) had thyroid dysfunction; of these, 51% (n=23) had Subclinical Hypothyroidism (SH), 36% (N=16) had pre-existing Overt Hypothyroidism (OH), 11% (n=5) were diagnosed with OH during pregnancy and 2% (n=1) had hyperthyroidism. Overall, 10% of pregnancies had SH compared to the 2-3% reported in the literature. The mean gestational ages at diagnosis for patients with SH and OH were 22 and 18 weeks respectively (2nd trimester). Type of DM, White's Class and initial HbA1c were not predictors for thyroid dysfunction. Being Caucasian was a significant risk factor (p=0.001).

In our patients with Pregestational Diabetes, we found a high prevalence of Subclinical Hypothyroidism compared to what is reported in literature. Thyroid dysfunction was often diagnosed in the 2nd trimester when most pregnancies complicated by DM have already been screened. We advocate universal screening for thyroid dysfunction during pregnancy more than once in order to identify patients who may benefit from treatment in order to minimize risks for adverse pregnancy outcomes.

2400-PO

WITHDRAWN

2401-PO

A Training Program for Women at Risk for Gestational Diabetes

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Moderate daily physical activity and exercise during pregnancy has been found to be associated with reductions in the risk of gestational diabetes mellitus (GDM).

In the FitFor2-study we aimed to assess whether an exercise program could improve fasting plasma glucose levels of women at high risk for GDM. In a randomised controlled trial, women at risk for GDM and who visited one of the participating hospitals or midwifery practices were eligible to participate. Women were considered to be at risk for GDM when they were obese (BMI > 30) or overweight (BMI > 25) AND had at least one of the three following characteristics: a) history of macrosomia (offspring > 4000g); b) history GDM during previous pregnancy; c) first grade relative with diabetes mellitus type 2.

After baseline, women were randomly allocated to in the intervention or control group. The intervention group received an exercise program twice a week in addition to usual care. The exercise program consisted of aerobic and strength exercises under close supervision of a physiotherapist. Data were collected at 15, 24 and 32 weeks of pregnancy and 12 weeks after delivery. Primary outcomes were fasting plasma glucose and birth weight.

A total of 124 women was randomised (61 usual care group and 63 intervention group). At baseline, no differences in maternal characteristics (age, BMI, education, ethnicity and parity) were present between the groups.

No significant differences were found between the intervention and usual care group regarding fasting blood glucose on the different measurement moments. Also no differences were found in blood glucose or area under the curve after a 100g oral glucose tolerance test. No significant differences were found between the intervention and usual care group regarding mean birth weight (3540 vs 3386 gram) or macrosomia (n=11 vs n=6). Compliance with the exercise program was low.

The results of the FitFor2-study showed that the exercise programme did not have significant effects on blood glucose levels or birth weight. Low compliance may explain the lack of effect of the exercise intervention.

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2402-PO

A1C and Postpartum Abnormal Glucose in a Cohort of Women with Gestational Diabetes

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Gestational diabetes (GDM) is a risk factor for type 2 diabetes. Hemoglobin A1c (A1C), a marker of glycemic control, may help identify women with GDM at high risk of postpartum glucose abnormalities. The study objective was to analyze the association between A1C at GDM diagnosis and impaired fasting glucose (IFG) / impaired glucose tolerance (IGT) during the postpartum period. This retrospective cohort study utilized medical records from women managed for GDM at the Carolinas Medical Center Diabetes and Pregnancy Program. Women eligible for this study had a singleton, live birth from November 2000-April 2010, and were diagnosed with GDM at ≥24 weeks gestation by a 3 hour 100 g oral glucose tolerance test (OGTT), a glucose challenge test ≥200 mg/dl, or a random blood glucose ≥160 mg/dl. A1C was measured at time of GDM diagnosis. The association of A1C at GDM diagnosis with postpartum maternal IFG and IGT was analyzed using a Weibull survival model. 717 records were reviewed, 321(45%) met the inclusion criteria. Of women with GDM 166(52%) completed a postpartum OGTT. We found 55(33%) had IFG, 47(28%) IGT, and 9(5%) type 2 diabetes. After adjustment for important covariates, women in the highest A1C quartile had a 29% higher risk of IFG (95% CI 0.70, 2.38) and a 47% higher risk of IGT (95% CI 0.81, 2.67) compared to women in the lowest A1C quartile. Higher A1C at time of GDM diagnosis is associated with increased risk of postpartum abnormal glucose; this association may be strongest with IGT.

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2403-PO

Angiogenin Is Not Increased in Patients with Gestational Diabetes

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Gestational diabetes mellitus (GDM) is a translational state of increased insulin resistance and accelerated atherosclerosis. Since angiogenin -an important growth factor involved in angiogenesis - is reduced in type 2 diabetes we were interested if alterations of angiogenin are already present in GDM and related to glucose metabolism and glycemic control.

We performed a cross-sectional and a longitudinal study, in which 35 patients with GDM (BMI 28.0± 5.7 kg/m², mean age 33±4 years) as well as 10 pregnant women without GDM (NGDM, BMI 28.7± 4.4 kg/m², mean age 31±5 years) were included and compared with 10 non-pregnant healthy controls (CO, BMI 24.1± 4.6 kg/m², mean age 35±10 years). An oral glucose tolerance test (75g) and HOMA insulin resistance were assessed at 28 weeks of gestation as well as 8 weeks postpartum. Blood samples for angiogenin were obtained at the same time points and were determined by an ELISA.

For author disclosure information, see page 785.

Angiogenin levels in GDM during pregnancy did not differ significantly from CO (722±142 vs 697±132 ng/ml). In addition, there was no difference in angiogenin between GDM and NGDM (722±142 vs 706±189 ng/ml). In the GDM patients as well as in the NGDM patients only small changes of angiogenin levels were obtained postpartum (GDM:710±152 ng/ml; NGDM: 737±127 ng/ml). During pregnancy patients with GDM and NGDM differed significantly in glucose 1 hour (187±30 vs 125±31 mg/dl; p<0.001) and 2 hours after the oral glucose load (153±31vs 109±24 mg/dl; p<0.001), but no correlation between angiogenin and glucose levels or HOMA insulin resistance was obtained.

Angiogenin levels were not different among pregnant women presenting with or without gestational diabetes and were similar as in healthy non-pregnant women. These findings indicate that angiogenesis - as evaluated by angiogenin levels – is not altered in patients gestational diabetes, a mild form of mainly postprandial diabetes.

2404-PO

Atlantic DIP: Diabetes and Stress during Pregnancy—A Comparative Psychological Study

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Diabetes in pregnancy affects 1-2% of pregnant Irish women and may increase the risk of maternal and perinatal morbidity and mortality. Management of diabetes can be a significant source of stress for patients and may be exacerbated when combined with the experience of pregnancy and worries about the unborn child. We carried out a prospective cross-sectional study which aimed to compare levels of psychological stress and wellbeing in pregnancy in women with pre-existing (Type 1 or Type 2) Diabetes (PDM), Gestational Diabetes Mellitus (GDM), and non-diabetic pregnant controls.

We studied 189 pregnant women; 23 with PDM, 76 with GDM and 90 healthy controls attending antenatal services. Stress levels were evaluated using several standardised psychological questionnaires; The Pregnancy Experience Scale; The Depression Anxiety Stress Scale; the Multidimensional Perceived Social Support Scale; the Illness Perception Questionnaire-Diabetes; the Diabetes Self-Efficacy Scale; the SF-8 and the Problem Areas in Diabetes Scale. We anticipated higher stress in diabetic women and a possible protective role of social support.

Our results show a non-significant trend of increased stress and lower quality of life among diabetic women compared to non-diabetic controls. Women with PDM also perceive their illness as having a higher impact on their lives than those with GDM, p<0.0001. The results of the remaining questionnaires demonstrate a general trend towards higher distress in diabetic women. There was also a trend towards higher perceived social support among the healthy controls which may confer a protective role against psychological stress.

Questionnaire	Pre-existing x̄ (S.Dev.) n=23	GDM x̄ (S.Dev.) n=76	Control x̄ (S.Dev.) n=90	Sig.	Test Stat. H=KW test F=ANOVA t=T-Test z=Mann U
PES: Pregnancy uplifts frequency	23.68 (7.82)	25.70 (9.01)	26.69 (8.24)	0.275	H=3.355.
PES: Pregnancy uplifts intensity	1.91 (0.43)	1.97 (0.39)	1.95 (0.43)	0.869	F(2,186)=0.141
PES: Pregnancy Hassles Frequency	15.96 (6.20)	16.11 (8.14)	17.82 (7.86)	0.235	H=2.081
PES: Pregnancy Hassle Intensity	1.63 (0.39)	1.57 (0.40)	1.59 (0.40)	0.705	H=0.654
PES: Composite ratio hassle to uplift frequency	0.80 (0.55)	0.78 (0.67)	0.75 (0.41)	0.669	H=1.675
PES: Composite ratio hassle to uplift intensity	0.88 (0.20)	0.83 (0.28)	0.84 (0.21)	0.305	H=3.057
DASS: Stress	12.09 (8.99)	12.40 (9.17)	11.82 (8.82)	0.913	H=0.912
DASS: Anxiety	7.26 (7.02)	7.86 (7.70)	7.71 (6.80)	0.671	H=0.065
DASS: Depression	5.78 (4.63)	7.87 (7.80)	5.71 (6.88)	0.386	H=3.556
MSPSS: Significant Other	25.96 (3.16)	25.41 (4.54)	25.93 (3.35)	0.833	H=0.770
MSPSS: Family	22.23 (6.08)	23.75 (5.17)	23.79 (4.90)	0.359	H=2.093
MSPSS: Friends	22.57 (4.20)	23.36 (4.90)	23.4 (4.11)	0.491	H=1.108
MSPSS: Total Social Support	69.59 (12.33)	72.68 (12.06)	73.66 (9.90)	0.326	H=2.531
BIPQ-Diabetes	42.52 (8.12)	30.44 (9.39)	-	**<0.0001**	t=6.02
DSES	6.91 (1.80)	5.93 (1.99)	-	0.032	t=2.22
SF8	13.70 (6.17)	13.99 (5.70)	11.84 (5.85)	0.271	F(2,186)=1.315
PAID-5	9.26 (6.26)	7.59 (5.21)	-	0.245	z=-1.16

These preliminary results suggest that pregnant diabetic women perceive themselves as having a lower quality of life and higher levels of stress in pregnancy than non-diabetic controls, however, further research is required.

2405-PO

BIAsp 30 Was Well Tolerated and Non-Inferior to BHI 30 in the Management of GDM: Findings from a Randomized Controlled Trial

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The objective was to compare the efficacy and safety of BIAsp 30 and BHI 30 in the management of gestational diabetes mellitus (GDM). In total, 163 women with GDM were assigned to BIAsp 30 (group A) and 160 to BHI 30 (group B). There was no statistically significant difference in maternal characteristics at entry between groups A and B, or in terms of glycemic control by onset of labor. The frequency of newborns with macrosomia was 6.3% in group A and 6.9% in group B; this difference was not statistically significant. By the last visit before labor, the required insulin dose was significantly lower for group A than group B (19.8±15.8 IU versus 26.3±23.2 IU respectively, p=0.006). In conclusion, BIAsp 30 was well tolerated and non-inferior to BHI 30 in the management of GDM, resulting in comparable fetal outcomes. Based on final doses, BIAsp 30 may offer a greater potential to treat to target in pregnant women.

Table 1. Maternal characteristics

Variable	Group A (BIAsp 30) (n=163)	Group B (BHI 30) (n=160)	*p*-value
Age (yr, median, range)	29.2±4.0	29.6±4.5	>0.05
Height (cm)	157.8±5.5	156.6±5.65	>0.05
Weight (kg)	67.3±11.0	66.2±12.15	>0.05
BMI	26.0±3.4	25.8±3.4	>0.05
Gestational week at diagnosis	19.3±6.3	19.9±7.1	>0.05
Gestational week at insulin initiation	21.7±9.3	22.4±10.1	>0.05
Maternal weight gain (kg)	10.3±2.5	10.8±3.1	>0.05
FPG at entry (mg/dL)	103.8±17.9	108.2±24.9	>0.05
FPG at labor onset (mg/dL)	93.0±14.4	95.4±19.0	>0.05
2 h PPG at entry (mg/dL)	164.7±38.7	163.8±48.1	>0.05
2 h PPG at labor onset (mg/dL)	127.6±29.0	127.0±29.9	>0.05
A1C at entry (%)	6.1±0.8%	6.2±1.0%	>0.05
A1C at labor onset (%)	5.8±0.6%	6.0±0.7%	>0.05

Table 2. Delivery and fetal outcomes

Variable	Group A (n=163)	Group B (n=160)	*p*-value
Cesarian section delivery (n, %)	144 (88.3%)	141 (88.1%)	>0.05
Gestational week at delivery	38.3±1.6	37.6±1.5	>0.05
Neonatal outcomes:			
Length (cm)	48.1±2.1	47.8±2.6	>0.05
Weight (kg)	3.2±0.4	3.2±0.5	>0.05
Percentile rank (%)			
0–10	10.6	11.9	
10–25	11.9	23.8	
25–50	23.1	21.9	
51–75	25.0	21.9	
75–90	23.1	13.8	
>90 (macrosomia)	6.3	6.9	0.82
Apgar score:			
1 min	8.1±0.5	8.0±0.5	>0.05
5 min	9.1±0.5	9.1±0.6	>0.05

2406-PO

Clinical Outcomes in Gestational Diabetes—A Retrospective Observational Study in 398 Patients at a German Single University Center

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Gestational Diabetes Mellitus (GDM) is associated with substantial rates of maternal and perinatal complications with rising prevalence. In a retrospective observational study we consecutively evaluated 398 women with GDM and impaired glucose tolerance (IGT), who were counselled, treated, and who delivered between 2002 and 2008 at the University Hospital

of Freiburg. Pregnant women were divided into three groups according to gestational age at diagnosis of GDM and IGT: group 1:< 27. week; group 2: 27. – 33. week; group 3: > 33. week). Observational results were compared to the country-wide Perinatal Registry of Baden-Württemberg (PR-Ba-Wü). One-third of the women were obese (27% with BMI > 30 kg/m², no difference between GDM/IGT and the three subgroups), but there was a significant larger weight gain in group 3 than in group 1 (19,8 kg vs. 11,3 kg). 57% of women with GDM required insulin therapy, but also 46% of women with initial IGT. Caesarean section rate was 57% (no significant differences between the three groups) and 30% in PR-Ba-Wü (p<0,001). The mean birth weight was 3340,8 g and 12,6% were heavier than 4000 g (no difference between GDM and IGT). Neanates of group 3 were significant heavier than neonates of group 1 (3586,8 g vs 3265,2 g; p=0,04). In groups 1-3, 39%, 30% and 26% of the neonates needed neonatal intensive care, and length of ICU stay was 6,16, 4,72 and 2,69 days, respectively. The three main reasons were hyperbilirubinemia, respiratory distress syndrome and hypoglycaemia. There was a significant higher rate of congenital malformations in group 1 (15%) as compared to group 3 (7%). After delivery, 72,7% of mothers had an oGTT, and 10 % were diagnosed with type 2 diabetes mellitus. In a questionnaire only 32% of GDM-women performed diabetes-preventive lifestyle changes after pregnancy.

These results confirm unfavourable outcomes, when GDM was present before week 27. Furthermore they indicate, that pregnant women with IGT must be counselled like women with GDM, because they need insulin in the course of pregnancy. Specific attention must be given to follow-up care, including oGTT and lifestyle changes to prevent type 2 diabetes mellitus in mothers.

2407-PO

Differential Response to Glucose during Pregnancy by Race/Ethnicity

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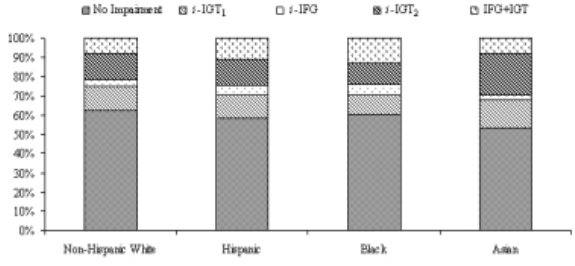
Different combinations of prenatal oral glucose tolerance test (OGTT) results may impact both short- and long-term risk for adverse maternal and offspring outcomes. We examined racial/ethnic differences in OGTT results for women with singleton pregnancies who delivered at southern California Kaiser Permanente in 1995-2009. Of 254,825 women who had a 50-g 1-hr glucose challenge test during pregnancy (27% non-Hispanic White, 49% Hispanic, 10% Black, 12% Asian), 70,141 (27%) subsequently had a 100-g 3-hr OGTT (23% non-Hispanic White, 53% Hispanic, 7% Black, 16% Asian). Based on these OGTT results, we used Carpenter-Coustan thresholds (FPG ≥ 95, 1-hr ≥ 180, 2-hr ≥ 155, 3-hr ≥ 140 mg/dl) to categorize women into five mutually exclusive groups: no glucose impairment; single isolated impaired glucose tolerance (*i*-IGT$_1$) if only one post-load value exceeded its threshold and FPG < 95 mg/dl; isolated impaired fasting glucose (*i*-IFG) if all post-load values were below their respective thresholds and FPG ≥ 95 mg/dl; double-isolated impaired glucose tolerance (*i*-IGT$_2$) if two or more post-load values exceeded their respective thresholds but FPG < 95 mg/dl; combined IFG and IGT (IFG+IGT) if any one post-load value exceeded its threshold and FPG ≥ 95 mg/dl. Overall, 58% of women had no impairment, 13% *i*-IGT$_1$, 4% *i*-IFG, 15% *i*-IGT$_2$, and 10% IFG+IGT. Asian women were more likely to have *i*-IGT$_1$ or *i*-IGT$_2$, and less likely to have *i*-IFG, than Black, Hispanic and non-Hispanic White women (figure; p<0.0001). Further stratifying by maternal age and parity resulted in a similar pattern of abnormal OGTT values by race/ethnicity. These data suggest that Asian women are more likely to have impaired response to glucose during pregnancy and may have a specific underlying metabolic defect that differentially confers risk for short- and long-term adverse outcomes compared to women of other race/ethnicities.



2408-PO

WITHDRAWN

2409-PO

Early Risk Determinants for Overt Diabetes after Gestational Diabetes

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Gestational Diabetes Mellitus (GDM) is associated with a high risk of type 2 diabetes, but as it comprises a heterogeneous population risk stratification and optimal therapeutic targets for diabetes prevention after delivery are unclear. Therefore, we aimed to assess a cluster of risk factors including parameters of the metabolic syndrome in women with GDM early after delivery that feature the best prediction for developing diabetes.

110 women with GDM 3-6 month after delivery received a complete metabolic characterisation at baseline as well as annually over 10 years of follow-up. We used cut-points for parameters characterizing the metabolic syndrome as well as demographic variables at baseline to predict diabetes manifestation.

Metabolic disturbances and insulin treatment during pregnancy were significantly associated with overt diabetes. Waist-circumference ≥80cm failed to show a significant impact on later development of the disease, however, reached significance when ≥88cm was used as cut-off value. We identified impaired glucose tolerance (IGT; HR:6.77, CI:2.96–15.45, p<0.001) as well as HDL-cholesterol <50mg/dl (HR:2.88, CI:1.24–6.67, p=0.010) and age >35 years (HR:3.06, CI:1.32–7.12, p=0.006) as the best predictors with additive effects: Women with at least 2 risk factors had a higher risk to develop the disease as compared to those subjects, who showed only one risk factor (HR:3.2, CI:1.4–7.7, p=0.008).

This study shows a strong association between parameters of the metabolic syndrome, in women with a recent history of GDM and diabetes manifestation. IGT, HDL-cholesterol <50mg/dl and age >35 years were identified as the best predictors.

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2410-PO

Effections of First Trimester Glucose and Lipids on Gestational Diabetes Mellitus (GDM)

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Aim: To evaluate whether the first trimester fasting glucose and lipids effects GDM and the outcomes of delivery.

Subjects and Methods: A total of 1175 pregnant women who underwent fasting glucose(FG), triglyceride (TG), cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid(UA) and sensitive C reactive peptide (sCRP) at first trimester and a standard 75-g oral glucose tolerance test (OGTT) between 24 and 32 weeks gestation during 2005-2009 in Beijing 306 Hospital of PLA were included in this retrospective analysis. The association of first trimester FG, lipids, sCRP and UA with GDM and the delivery outcomes were analysis.

Results: 328 GDM were included in this study. First trimester FG (4.32±0.62 vs 4.13±0.45 mmol/l, p<0.01), TG (1.95±0.79 vs 1.75±0.80 mmol/l, p<0.01)and sCRP(2.36±1.39 vs 2.1±1.58 mg/l, p<0.05) were higher in GDM than those in non-GDM. First trimester fasting glucose, TG and sCRP were positive correlated with glucose levels during OGTT. Both TG and sCRP positive correlated with TC, LDL-C, UA, but negative correlated with HDL-C. First trimester FG negative correlated with the neonatal VirgiriaApgar score. With the rise in FG, TG and sCRP of pregnancies in the first trimester, Caesarean section rates increased. For the data of the 1175 pregnancies, we calculated adjusted odds ratios for GDM and the adverse delivery outcomes associated with first trimester FG, TG, sCRP. For GDM, the odds ratios were 1.77 (95% confidence interval [CI], 1.76 to 2.46), 1.23 (1.01 to 1.50), and 1.09 (0.98 to 1.21), for neonatal respiratory distress, 2.55 (95% CI, 1.55 to 4.46), 0.50 (0.21 to 1.19), and 1.17 (0.95 to 1.44); for macrosomia (>4000g), 1.42 (95% CI, 1.01 to 2.00), 1.22 (0.97 to 1.53), and 1.08 (0.96 to 1.08); for low birth weight baby (<2500g), 1.32 (95% CI, 0.82 to 2.14), 1.39 (1.04 to 1.87), and 1.01 (0.81to 1.25).

Conclusions: First trimester FG, TG and sCRP were increased in GDM, even in the normal range, the higher level of them are the risk factors for GDM, and may effect the worse outcomes of delivery.

For author disclosure information, see page 785.

2411-PO

Glycemic Control in Post-Pregnancy Follow-Up in Type 1 Diabetes Women

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Tight glycemic control is essential during pregnancy complicated by type 1 diabetes mellitus (T1DM) in order to improve the prognosis for the mother and child. Most women with T1DM are able to significantly lower their glucose levels during the pregnancy. However, very few data exists on their glycemic control after the delivery.

The purpose of this observational study was to assess glycemic control in T1DM women after the pregnancy.

We examined medical records of 364 consecutive singleton pregnancies in women with pregestational T1DM who received medical care in the Department of Metabolic Diseases, Krakow, Poland between 1999 and 2010. We found 213 subjects that had been receiving an intensive diabetes management program during pregnancy and had had at least one follow-up visit with HbA1c measurement after the delivery. We analysed HbA1c level in the 1st trimester (reflecting pre- and early pregnancy periods), the 3rd trimester, and the last post-pregnancy follow-up measurement (mean 8.6 months ±15.4 post delivery).

The mean age of the examined women was 27.7 years ±4.6, duration of T1DM- 12.0 years ± 7.9. The mean initial HbA1c level was 6.9% ± 1.3. We observed a significant improvement in HbA1c level, which reached 5.7% in the 3rd trimester (5.7 % ±0.7; p<0.000001). At the post-pregnancy follow-up, we noticed a substantial rise in HbA1c (by 1.1%). This was significantly higher than in the last trimester (p<0.00001) but not different from the initial value (p=0.1). Subjects who after pregnancy were on continuous insulin infusion (n=82) showed a smaller rise than those on multiple daily injections (n=131) (mean 6.4 % ±1.0 vs. 6.9.0 ±1.6; respectively p=0.0038). When we compared data from follow-ups that took place less than 12 months after delivery (179 measurements) and those after this cut-off point (34 measurements), we found no difference in HBA1c values (6.65 vs. 6.94; p=0.3).

In conclusion, in this, so far the largest, clinical observation, T1DM women showed a substantial deterioration in post-pregnancy glycemic control. The magnitude of this deterioration seems to depend on the treatment method.

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2412-PO

Hyperglycemia Alters Proliferation of Human First Trimester Trophoblast-Derived ACH-3P Cells in an Oxygen-Dependent but ROS-Independent Manner

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Diabetes in pregnancy is associated with reduced embryo size at the end of the first trimester, known as early fetal growth delay. Placental and fetal sizes are tightly associated, which suggests also impaired placental growth. This notion is supported by reduced maternal levels of placental lactogen in first trimester of T1D pregnancy. Increased production of reactive oxygen species (ROS) in pregnancy which is exacerbated in diabetes may affect placental development. We hypothesize that increased ROS levels associated with hyperglycemia of diabetes result in reduced trophoblast growth, which can be prevented by antioxidants.

First trimester trophoblast-derived cell line (ACH-3P) was cultured under hyper- and normoglycemia (HG: 25 vs NG: 5.5 mM D-glucose) and different oxygen conditions (2.5, 8 and 21%) up to 72 h. Proliferation was measured by counting viable and dead cells. Oxidative stress was measured by a fluorescence assay (H_2DCFDA).

Already after 24 h cells produced significantly more ROS under HG at 2.5, 8 and 21% oxygen. After 72 h at 21% oxygen HG resulted in 60% fewer viable cells (p<0.001), whereas dead cell number was unaffected. FACS analysis showed significant modifications in cell cycle (G_1 and S phase) under HG at 21% oxygen. However, at 2.5 and 8% oxygen cell proliferation and cell cycle were unaltered under HG. Addition of the antioxidants vitamin C, vitamin E (Trolox) and NAC did not restore proliferation under HG at 21% oxygen. Reduction of intracellular ROS generation by inhibition of xanthine and NADPH oxidase using allopurinol and apocynin/VAS-2870, respectively, did not alter proliferation under HG at 21% oxygen. Increasing mitochondrial superoxide production by antimycin A and oligomycin had no effect on cell growth under HG at 21% oxygen.

Proliferation of ACH-3P cells is reduced under HG only at 21% oxygen, because of changes in the cell cycle in G_1 and S phase. ROS levels and cell proliferation are not associated in ACH-3P cells under the conditions used.

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2413-PO

Hypoadiponectinemia during Early and Late Pregnancy Is Associated with an Increased Risk of Gestational Diabetes Mellitus and Mild Gestational Hyperglycemia in Young Pregnant Women

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Lower maternal plasma adiponectin concentration is associated with an increased risk of gestational diabetes mellitus (GDM). We hypothesized that a similar relationship would be found with mild gestational hyperglycemia. In a nested case-control study of pregnant women (African-American 35%, Hispanic 47%, Caucasian 18%) aged 23.1±0.2 (yr), pregravid BMI (kg/m^2) 26.3±0.2 in 3 groups including GDM (N=80), positive glucose challenge test and normal diagnostic oral glucose tolerance test (positive GCT non-GDM, N=128) and normal GCT (controls, N=557), serum adiponectin concentrations were measured at entry (16 wks) and the 3rd trimester (30 wks) by ELISA.

Serum adiponectin concentration (µg/l) at entry was significantly decreased in GDM (11.5±0.6) and in positive GCT non-GDM (13.2±0.5) when compared to controls (14.7±0.3, p <0.05 for each). During the 3rd trimester, adiponectin concentration was decreased in all groups compared to entry, the inverse relationship between adiponectin and hyperglycemia remained the same as at entry and was statistically significant.

Multiple logistic regression analysis adjusted for BMI, age, parity, ethnicity and cigarette smoking showed that the low adiponectin concentration (the lowest tertile, <10.7 µg/l at entry) was associated with a 2-fold increased risk of GDM (adjusted odds ratio (AOR) 2.03, 95% confidence interval (CI) 1.21-3.42 and a 53% increased risk of positive GCT non-GDM (AOR 1.53, 95% CI 1.03-2.34, p for trend <0.001). During the 3rd trimester, similar associations between low adiponectin (the lowest tertile, <9.0 µg/l) with GDM (AOR 2.14, 95% CI 1.27-3.61) and with positive GCT non-GDM (AOR 1.64, 95% CI 1.08-2.48, p for trend <0.0001) were observed.

Our data suggest a strong association between hypoadiponectinemia and the risk of overt GDM as well as of less severe gestational hyperglycemia without GDM. This association was independent of maternal adiposity.

Supported by: NIH

2414-PO

WITHDRAWN

2415-PO

Maternal and Neonatal Outcomes in Pregnancies Complicated by Gestational Diabetes Mellitus in Denmark from 2004 to 2010

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In 1989, the St. Vincent Declaration set as a goal that the outcome of pregnancies complicated by diabetes should approach those without diabetes. The aim of this study was to analyze the outcome of GDM pregnancies in Denmark from 2004 to 2010 and compare it with the background population.

A population-based study on a cohort consisting of all Danish women giving birth to a singleton from 2004 through 30 June 2010 (n = 402,959) was undertaken. The women were identified from the National Birth Registry (NBR) in which all deliveries in Denmark are registered. The database contains data on 99.8% of all deliveries in Denmark with a population of more that 5 million. The diagnostic criterion for GDM was a 2 h blood glucose ≥ 9 mmol/l at a 75 g oral glucose tolerance test.

The final study population consisted of 398,623 women, of which 9014 had GDM (2.3%).

Adjusted odds ratios (OR) for GDM vs. controls were: pre-eclampsia, 1.30 (95 % confidence interval (CI) 1.20-1.41); Caesarean section (elective) 1.07 (1.01-1.14); Caesarean section (emergency), 1.11 (1.04-1.18); shoulder dystocia, 1.72 (1.40-2.11); birth weight > 4.500 g, 1.40 (1.23-1.59). No difference was seen with respect to post partum haemorrhage, thrombosis, Apgar < 7 at 5 min or stillbirth.

Women with GDM have higher risk of pre-eclampsia, Caesarean section (elective and acute), shoulder dystocia and birth weight > 4.500 g. Consequently, Denmark has not reached the goals of the St Vincent Declaration.

2416-PO

WITHDRAWN

2417-PO

Mother-Daughter Magnesium, Glycemic Status and Metabolic Parameters 15-Years after Gestational Diabetes

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Hypomagnesemia has been documented in type 2 diabetes; however, associations between serum magnesium (Mg), glycemic status, and metabolic parameters have been inconsistent. A comprehensive cross-sectional study involving lifestyle assessment and clinical indices, including an oral glucose tolerance test, was conducted 15-years post-partum in women affected by gestational diabetes mellitus (GDM) (n=72), women who were normoglycemic during pregnancy (n=94) and their teenage daughters (n=166). At follow up, 33.3% of mothers with a history of GDM and 5.3% of non-GDM subjects had type 2 diabetes (diagnosed, or fasting glucose ≥ 7mmol/l, or OGTT 2hr glucose ≥ 11 mmol/l). In multivariate linear regression models including all mothers, GDM status (B= -0.53, SE=0.19, p=0.01) and race (B= -0.05, SE=0.23, p=0.03) were associated with serum Mg, but not age (p=0.18), BMI (p=0.46), current impaired fasting glucose (p=0.26) nor type 2 diabetic status (p=0.19). Serum Mg (B= -0.61, SE=0.24, p=0.01) and GDM status (B= 0.15, SE=0.06, p=0.12) were significantly associated with LDL, but not BMI, WC, age, race, diabetic status, nor HOMA IR (p>0.05). In logistic regression models, serum Mg [0.03 CI (0.01-0.85)] and diabetic status [3.55 CI(1.18-10.72)] were significantly associated with odds of low HDL (<1.29 mmol/l), while age, race, GDM status, BMI, and HOMA IR were not significant (p>0.05). Serum Mg was not associated with mothers' or daughters' 120 min OGTT glucose or insulin (p>0.05). Among non-diabetic mothers, however, serum Mg was significantly associated with the insulinogenic index (B= -1.35, SE=0.646, p=0.04) in models adjusted for age, race, BMI, and GDM status. Daughter's serum Mg at age 15 is associated with mothers' GDM status (B= -0.06, SE=0.02, p=0.00) and her own degree of insulin resistance (HOMA IR) (B= -0.01, SE=0.005, p=0.03), but not her BMI, race, mother's serum Mg, nor mother's diabetic status (p>0.05). Thus, serum Mg and GDM status are significant covariates in models with metabolic outcome variables (LDL, HDL, insulinogenic index). In mothers and daughters, serum Mg is significantly associated with mothers' GDM status, independent of mothers' current diabetic status.

2418-PO

WITHDRAWN

2419-PO

Perinatal Outcomes in Obese, Over- and Normal- Weight Pregnant Women with GDM (Gestational Diabetes Mellitus) Treated with Detemir and Aspart

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Obesity and GDM are well-known independent risk factors for excessive fetal growth and their association has a cumulative effect. A thigh metabolic control is of primary importance for a good maternal-fetal outcome. Objective: To evaluate fetal outcomes in a group of obese, over- and normal-weight women with GDM treated with insulin Detemir and Aspart. Methods and partecipants: The study includes 81 women with GDM diagnosed in accordance with Carpenter and Coustan's standards divided in 3 groups based on the BMI (46 normalweight with BMI <25; 20 overweight with BMI 25-29 and 15 obese with BMI> 29).Pregnant women were treated with multiple daily injections of Detemir and Aspart and glucose levels were measured with Accu-Chek Active glucometer. Results: We didn't find any significant difference in fetal outcomes between normal-weight and obese/overweight women (gestational age at delivery: 38,9 ± 1,8 vs 38,9 ± 1,9 weeks; birthweight: 3232 ± 605 vs 3197 ± 120 gr; rate of macrosomia: 6,5% vs 8,5%; rate of LGA (Large for Gestation age): 2,1% vs 5,7%; mean PI (Ponderal Index): 2,65 ±0,3 vs 2,7 ±0,2; rate of PI> 2,85: 23,9% vs 25,7%; rate of non elective cesarean delivery: 13% vs 14%). Furthermore there were no significant differences in total and weekly mean glycemic levels between normal- and obese/overweight women (fasting: 87 ± 7,48 vs 88 ±8,6 mg/dl total, 88 ±6,9 vs 86 ±8,3 mg/dl between 27th-32th weeks, 86 ±8,3 vs 86 ±8,2 mg/dl >32th week; 1 hour postprandial: 118 ±11,5 vs 120±12,2 mg/dl total, 122 ±14 vs 119 ±11,9 mg/dl 27th-32th, 18 ±12,1 vs 119 ±12,5 mg/dl >32th; 2 hours postprandial: 101 ±9,9 vs 103 ±10,7 mg/dl total, 104±12,7 vs 101 ±10,6 mg/dl 27th - 32th, 100 ±10,8 vs 100 ±9,2 mg/dl >32th. Conclusions: In our experience Detemir insulin seems to be able to control diurnal and nocturnal glucose levels also in overweight and obese women. Our results show that glucose levels achieved in all women are lower than threshold proposed by Jovanovic and coll. (fasting <90 mg/dl, 1 hour postprandial <120 mg/dl); these levels allowed a reduction of LGA despite a still high rate of PI>90° percentile.

2420-PO

Postnatal Blood Glucose Screening in Gestational Diabetes (GDM)

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GDM is any degree of glucose intolerance with onset or first recognition during pregnancy. As GDM may not resolve after delivery postpartum surveillance is required but there is lack of agreement on the optimal methodology. In the UK, National Institute for Health and Clinical Excellence guidelines advise that GDM should be diagnosed using a 2-hr 75g oral glucose tolerance test (OGTT). Postpartum screening guidance is a single fasting plasma glucose (FPG) at 6-weeks to exclude hyperglycaemia with annual testing thereafter. As women with GDM are often from mixed ethnic groups and frequently have postprandial hyperglycaemia a 2-hr OGTT result may be more relevant.

Our study was undertaken to ascertain whether postpartum screening of FPG alone would miss patients with pre-diabetes or impaired glucose tolerance (IGT). Retrospective analysis of 138 women diagnosed with GDM using 75g OGTT (2008-2010) was performed. GDM was diagnosed if FPG was >6.0 mmol/L (108 mg/dl) or 2-hr value was ≥7.8 mmol/L (140 mg/dl). The incidence of GDM was 1.65%. In 24 patients a FPG of >6.0 mmol/L was observed (7.1 ± 0.2, mean ± SEM) whilst all patients had a 2-hr value ≥7.8 mmol/l (9.8 ± 0.2). Reclassification using IADPSG criteria revealed that 106 women in this cohort would fulfill a diagnosis of GDM. Of these 8% had elevated FPG alone ≥5.1 mmol/l (92mg/dl), 34% had an abnormal 2-hr glucose alone ≥8.5mmol/l (153 mg/dl) and 58% had both.

All women were invited for a 6-wk postpartum OGTT and 85% attended. Frank diabetes was diagnosed in one. All other women screened had a normal FPG but 15% had IGT on 2-hr values (9.0 ± 0.2 mmol/L). 83% of women with postnatal IGT were of Asian or African origin.

Table 1. Post-natal screening comparing FPG and 2-hr values.

FPG (mmol/L)	2-hr plasma glucose (mmol/L)		
	<7.8	7.8-11.1	>11.1
≤6	98	13	-
6.1-6.9	-	5	-
≥7	-	-	1

During 75g OGTT (n=117)

GDM was diagnosed most commonly on elevated 2-hr glucose rather than FPG. Using FPG alone for screening in the post-natal period is illogical and misses a substantial number of cases of women with IGT. As post-prandial hyperglycaemia is associated with increased cardiovascular risk, lifestyle advice and closer surveillance of these women is necessary.

2421-PO

Postocclusive Reactive Hyperemia in Women with a History of Gestational Diabetes

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Postocclusive reactive hyperemia (PORH) is a complex microvascular reaction that thought to be a marker of endothelial function. In the present study we aimed to investigate correlates of the PORH-index (PORHi) among women with a history of gestational diabetes (GDM) 3.3±0.5 (mean±SD) years after delivery.

This is a case-control study of 40 prior GDM cases and 28 controls that had normal glucose tolerance during pregnancy (age: 36.9±4.0 vs. 34.8±2.9 yrs, P=0.013, BMI: 27.2±6.5 vs. 24.7±5.0 kg/m², P NS). Participants filled in a

For author disclosure information, see page 785.

questionnaire followed by a clinical examination including anthropometrics, blood pressure, and blood draws for fasting lipids, and glucose measures during a 75g OGTT. Endothel-dependent vasodilatation was measured using a laser-Doppler flowmeter. The main outcome was the PORHi (the percentage increase in cutaneous blood flow from resting conditions to peak dilation following a 2 min upper arm occlusion).

The PORHi was lower in prior GDM cases than in controls (3.23±0.97 vs. 3.80±1.18; P=0.032). The prior GDM group had a higher waist to hip ratio (0.82±0.07 vs. 0.78±0.06), blood pressure (125±17/79±11 vs. 116±14/72±12 mmHg), HbA1c (5.6±0.3 vs. 5.4±0.3%), fasting (5.7±0.9 vs. 5.2±0.5 mmol/l) and 2-hour glucose (7.2±2.4 vs. 5.6±1.2 mmol/l), and 2-hour insulin (82±62 vs. 43±28 μIU/ml, all P<0.05). Negative correlation (all P<0.05) was found between the PORHi and prior GDM status (r=-0.253), white blood cell count (WBC, r=-0.278), lipoprotein(a) (lp(a), r=-0.248), 2h insulin (r=-0.252), and diastolic blood pressure (r=-0.259); while the PORHi was positively related to serum total cholesterol (r=0.278; P=0.022). According to a multiple linear regression model that explains 23% of the variation in the outcome, the PORHi was independently related to prior GDM status, WBC, lp(a), and serum total cholesterol.

We found that prior GDM women had impaired endothelial function. Furhtermore lower (pathological) PORH-index was related to higher white blood cell count and lipoprotein(a) suggesting that subclinical inflammation and the coagulation system are both involved in the development of microvascular endothel dysfunction.

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2422-PO

Pregnancy in Women with Type 2 Diabetes from Poland. The Impact of Pregnancy Planning and a Comparison with Type 1 Diabetes Subjects

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The number of pregnancies complicated by type 2 diabetes mellitus (T2DM) is growing, however, their clinical characteristics remain incomplete.

We aimed to assess clinical characteristics and selected pregnancy outcomes in pregestational T2DM from Poland and to compare them with those of T1DM. The impact of pregnacy planning was also analyzed.

We included 415 consecutive singleton pregnancies; among them, there were 70 women with T2DM and 345 with T1DM.

As compared to T1DM patients, women with T2DM were older (mean age 33.1 years vs. 27.8, respectively), heavier before pregnancy (mean BMI 30.8 kg/m^2 vs. 23.9), and had a shorter duration of diabetes (mean 3.3 years vs. 11.4); (p<0.0001 for all comparisons). The gestational age at the 1st visit was higher in T2DM (mean 11.4 weeks vs. 8.6; p=0.0004). Nevertheless, they had better glycemic control in the 1st trimester (mean HbA1c 6.2% vs. 7.0; p=0.003); in subsequent months the differences in HbA1c were no longer significant. T2DM women gained less weight during pregnancy (mean 9.9 kg vs. 14.1; p<0.0001). The proportion of combined outcomes (miscarriages, preterm deliveries, infant deaths, and congenital malformations) were similar in both groups (27.1% vs.28.1%; p=0.87) as was the frequency of caesarean sections (58.7% vs. 64.1%; p=0.30). Macrosomic babies were more than twice less frequent in T2DM and the difference reached borderline significance (7.9% vs. 17.5%, p=0.07). Pregnancy planning in T2DM had a significant impact on HbA1c in the 1st trimester (5.7% vs. 6.4% in the planning vs. the not planning group, p=0.02); the difference was not significant in the 2nd and 3rd trimester.

In conclusion, T2DM women had better glycemic control in the 1st trimester than T1DM subjects and gained less weight during pregnancy. This could have been the reason for the lower number of macrosomic babies but did not affect other outcomes. In T2DM, pregnancy planning had a beneficial glycemic effect in the 1st trimester.

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2423-PO

Prepartum BMI, Intrapartum Insulin Resistance, and Higher Intrapartum Systolic Blood Pressure Predict Post Partum Dyslipidemia in Women with Gestational Diabetes

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Gestational diabetes mellitus (GDM) predicts type 2 diabetes and hypertension but the associated dyslipidemia risk is less clear. In any pregnant woman, serum total cholesterol and triglycerides may increase during the second and third trimester, but whether the degree of increase predicts post partum dyslipidemia is uncertain. We hypothesized that among women with GDM, elevated intra-partum lipid values would predict postpartum dyslipidemia. We identified women who delivered a live birth at the Royal Victoria Hospital (Montreal, Canada) between 1 January 2007 and 31 December 2008 and had (1) GDM (2) assessment of serum lipids and insulin resistance at or after 26 weeks gestation and (3) a post partum lipid profile. The "exposures" of interest were an intrapartum triglyceride level of ≥ 2.5 mmol/l and/or total cholesterol/HDL ratio of ≥ 5.1. The outcome was a post-partum total cholesterol/HDL ≥ 4.0. Other potential predictors considered were pre partum BMI, intrapartum insulin resistance (HOMA-IR) and blood pressure, age, gravida, diabetes family history, and ethnicity. Intrapartum triglycerides and total cholesterol/HDL were considered in separate models. Among the 46 subjects identified, 23 had post partum dyslipidemia. In unadjusted analyses, neither intrapartum total cholesterol/HDL (Odds ratio, OR 1.28, 95% CI 0.66 to 2.45) nor triglycerides (OR 1.26, 95% CI 0.82 to 1.92) were conclusively associated with post partum dyslipidemia. In adjusted analyses, the most robust predictor was pre partum BMI (OR 1.8, 95% CI 1.2 to 2.6); intrapartum HOMA-IR (OR 1.1, 95% 1.0 to 1.3) and systolic blood pressure (OR 1.1, 95% CI 1.0 to 1.2) also appeared predictive (models adjusted gravida, pre partum BMI, HOMA-IR, and systolic blood pressure). Among women with GDM, pre partum BMI is the most important risk factor for post partum dyslipidemia. Insulin resistance itself has some contributory role. Targeted dietary and exercise interventions may be particularly important among obese/overweight women with a GDM history.

2424-PO

Public Health Surveillance of Gestational Diabetes Using Electronic Health Data

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Gestational diabetes (GDM) is a priority for public health surveillance and intervention as it carries both acute perinatal and chronic metabolic risks for mother and child and rates are increasing worldwide. Electronic health records (EHR) have considerable potential for GDM surveillance as they provide laboratory data for case identification, patterns of care, and metabolic outcomes in conjunction with race/ethnicity and body mass index (BMI), two important determinants of GDM risk.

We describe a project that identifies women with GDM via the EHR and sends reports of incidence, demographics, screening, and patterns of care to the Massachusetts Department of Public Health. The EHR Support for Public Health (ESP), system (http://esphealth.org) is a generalizable surveillance platform that can extract structured data from any EHR, run analyses, and transmit summary data to public health agencies. Using validated algorithms for detection of GDM, we queried EHR data of Atrius Health, a multisite ambulatory care organization with over 600,000 patients.

From 04/2006 to 11/2010, 822 pregnant women met criteria for GDM. Data on race/ethnicity was available for 716 (87%) of women. The highest prevalence of GDM was in Asian women (7/100 pregnancies), followed by Hispanic (4/100), Non-Hispanic Black (3/100) and Non-Hispanic Caucasian (2.5/100) women.

BMI was lower (p<0.0001) in Asian women (mean 25.6) than in other groups (mean BMI's 31-33). Only 26% of women had post-partum OGTT screening for diabetes. Of these, Asian women were the most likely to undergo testing (39%), and Hispanic women the least (6%). Among women tested, 36% had values consistent with diabetes (≥ 200mg/dl), suggesting that the women who do get tested are at high clinical risk. However, interpretation of post-partum diabetes rates by ethnicity is limited by the low number of Hispanic or Black women who underwent testing. We conclude that automated assessment of EHRs allows timely assessment of trends in rates of GDM and quality of care, including pre and post-partum screening, by race/ethnicity and BMI.

2425-PO

Risk of Hypertension after the Gestational Diabetes: Findings from a Large Multi-Ethnicity Cohort Study in Louisiana

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Gestational diabetes mellitus (GDM) was associated with an increased risk of gestational hypertension and preeclampsia. However, it is unknown whether a history of GDM increases the risk of hypertension after the index pregnancy. The objective of this study was to examine the association between the history of GDM and the risk of incident hypertension among 26,749 women from a large hospital cohort in Louisiana. Of them, 27.6%

For author disclosure information, see page 785.

were non-Hispanic white, 62.8% were African Americans and 9.6% were other race. Women were excluded from the current analyses if they had diabetes, hypertension, coronary heart disease (CHD), or stoke before the diagnosis of GDM. Follow-up of each woman continued until the date of the diagnosis of hypertension, or June 30, 2010. Women were also excluded during the follow-up if they developed any cardiovascular event before the diagnosis of hypertension. Cox proportional hazard regression model was applied to estimate the hazard ratio (HR) and 95% confidence interval (CI) for development of hypertension with controlling for potential confounders. We identified 1,514 (4.0%) women with a history of GDM (ICD-9: 648.8). During a median follow-up of 6.3 years, there were 4,522 (19.0%) incident cases of hypertension in the non-GDM group and 524 cases in the GDM group (34.6%). GDM was associated with an increased risk of hypertension in both age- and multivariate-adjusted models. After adjustment for age, race, income, smoking and body mass index (BMI), women with a history of GDM had a HR of 1.67 (95% CI: 1.53, 1.84; P < 0.0001) compared to women without GDM. Stratified analyses based on women's race (whites and African Americans) and BMI status (normal weight, overweight, and obese) yield similar results. Additional adjustment for having diabetes before the diagnosis of hypertension slightly attenuated the association but remained statistically significant (HR: 1.53; 95% CI: 1.39, 1.68; P < 0.0001). Results from this large multi-ethnicity cohort study indicate that women with a history of GDM have an elevated risk of developing hypertension in later life compared to women without GDM.

2426-PO

Serum Adipocytokines Concentrations and Insulin Resistance across Various Degrees of Glucose Tolerance in Pregnancy

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Adipocytokines are thought to be associated with insulin resistance (IR) in humans, while pregnancy is normally characterized by progressive IR. The degree of IR in pregnancy is further accentuated in women with gestational diabetes mellitus (GDM). The aim of our study was to evaluate the correlations between serum concentrations of different adipocytokines: adiponectin, leptin, resistin, retinol-binding protein 4 (RBP4), visfatin and degree of IR in different stages of glucose tolerance in pregnancy, using homeostatic model assessment of IR (HOMA-IR) as a reference.

After 100-g oral glucose tolerance test (OGTT), 74 pregnant women were divided into three groups: (1) controls (n=25) with normal glucose response; (2) an intermediate group (n=19) with impaired glucose tolerance and (3) GDM group (n=30). Fasting glucose and insulin samples were collected from all participants before starting OGTT. Adiponectin, leptin, resistin, RBP4 and visfatin concentrations were measured using ELISA kits. IR was assessed by HOMA-IR. Results are presented as median with interquartile range. Differences between groups were tested using ANOVA and Kruskall-Wallis test.

All groups were comparable regarding age, week of gestation and body mass index before gestation (BMI). Median age was 30 (28-34) years, median week of gestation was 27 (24-29) and median BMI was 22,7 (20.8-26.8) kg/m2. There were statistically significant differences in HOMA-IR (p=0.02), with medians 1.3 (0.8-1.8), 1.8 (1.2-3.0) and 2.0 (1.3-2.6) in groups 1, 2 and 3, respectively. However, no significant differences were found between the groups regarding adiponectin (p=0.88), leptin (p=0.76), resistin (p=0.11), RBP4 (p=0.33) and visfatin (p=0.53). Also, there were no differences in adiponectin/leptin ratio between the groups (p=0.70).

Adiponectin, leptin, resistin, RBP-4 and visfatin do not correlate with severity of IR, measured by HOMA-IR, across various degrees of glucose tolerance in pregnancy. Thus, these adipocytokines are not markers sensitive enough to replace HOMA-IR in pregnancy.

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2427-PO

Sleep-Disordered Breathing Is Common in Gestational Diabetes Mellitus

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Sleep-disordered breathing (SDB) describes a number of disorders that are characterized by abnormalities of respiratory pattern. Obstructive sleep apnea (OSA) is the most common of such disorders and is characterized by episodes of airflow limitation that lead to frequent, intermittent hypoxia. The average number of apneas and hypopneas per hour of sleep is the apnea-hypopnea index (AHI) with ≥5 events being diagnostic. The prevalence of OSA is estimated to be 5-11% among pre-menopausal women but the occurrence of SDB among women with gestational diabetes mellitus (GDM) is unknown. We hypothesized that women with GDM would have SDB that resolved post-partum. Participants (n=30; all diagnosed with GDM) in this study (aged 32±4 (mean±SD) years) wore a portable sleep recorder in their home at 30-34 weeks gestation and 2-3 months post-partum. Table 1 shows that 40% of the women had SDB. The current BMI of those with SDB was higher.

	SDB (n=12)	No SDB (n=18)	p-value
Fructosamine (µmol/L)	178±15	181±15	0.61
AHI (events/h)	10.1±4.6	1.3±1.2	<0.001
Nadir of oxygen saturation (%)	86.5±5.1	90.7±3.1	<0.05
BMI (kg/m^2)	41±8	32±6	<0.01
Epworth sleepiness score	8.4±5.8	7.7±3.7	0.69

Table 2 shows the percentage of maternal (e.g., preterm labor, preeclampsia) and neonatal complications (e.g., hypoglycemia, hyperbilirubinemia).

	SDB (n=12)	No SDB (n=18)	p-value
Gestational age at delivery (weeks)	38.8±1.4	38.6±1.2	0.41
Apgar at 1 minute	8.3±0.5	7.6±1.0	<0.05
Apgar at 5 minutes	8.9±0.3	8.7±0.5	0.12
% with at least 1 maternal event	17%	39%	0.25
% with at least 1 neonatal event	36%	50%	0.70

Complications appear to be more related to the presence of GDM than SDB. At follow-up (64±10 days post-partum), SDB had resolved for 4 individuals. This indicates that for approximately 15% of the women, SDB appeared to have developed during pregnancy. Whether those with non-resolving SDB represent a group with a very early propensity for the development of type 2 requires follow-up. These preliminary results indicate that SDB is a frequent co-morbid condition of GDM.

2428-PO

Socio-Economic Background and Travel Distances Affect Attendance Rates for Screening for Gestational Diabetes

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The link between socioeconomic disadvantage and poor health has been observed repeatedly. Gestational Diabetes affects up to 12% of pregnancies.

Diagnosis and subsequent treatment of this condition decreases fetal and maternal morbidity.

This study was completed by the Atlantic Diabetes in Pregnancy partnership, which offered universal screening for Gestational Diabetes at 24-28 weeks gestation. Data was collected on women who delivered in 5 antenatal centres between 2007 and 2009. Distance to antenatal centres was analysed using 'geocoding'. The calculated socio-economic background is based on a deprivation index derived from area of residence and national census data. The Deprivation Index is scored from 1-5, from least to most deprived, using various indicators; education, employment, percentage skilled/unskilled workers, demographic information, lone parents and number of persons/room.

9842 women were offered screening, of whom 5436/55% attended and 4406/45% did not attend. Using a logit model, the probability of attending for screening is reduced by 1.8% [95% CI: 1.3% to 2.3%] for every additional 10kms required to travel for screening, p=0.000. Using correlation studies, those women deemed 'most deprived' were 15% less likely to attend for screening than their 'least deprived' counterparts, p=0.0001.

Older women, those with a family history of diabetes and women from larger urban areas were more likely to attend for screening.

Women from lower socio-economic backgrounds and those who live further from antenatal centres are less likely to attend for screening for Diabetes in pregnancy.

2429-PO

The Increasing Prevalence of Diabetes in Pregnancy in White, Black and Hispanic Women in South Carolina, 1996-2008

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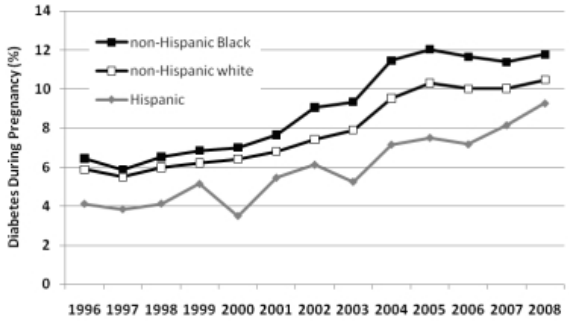
Our objective was to examine the prevalence of diabetes during pregnancy in non-Hispanic white (NHW), non-Hispanic black (NHB) and Hispanic women at the population level in South Carolina from January 1996 through December 2008. The study included 387,720 NHW, 232,278 NHB and 43,454 Hispanic live singleton births. Maternal inpatient hospital discharge codes from delivery were linked for 91.6% of births and prenatal

For author disclosure information, see page 785.

information was available for 48.2% of births (i.e., Medicaid or State Health Plan recipients). Diabetes during pregnancy included gestational and pre-existing and was defined by prenatal and maternal inpatient ICD-9-CM diagnostic codes (i.e., 64801-64802, 64881-64882 or 25000-25092) or report on the birth certificate. The overall prevalence of diabetes during pregnancy from any source was 8.2%; birth certificates identified 4.3%; hospital discharge identified 4.6%; and prenatal data identified 4.6%. Among those with prenatal data available, 10.9% had diabetes from any source with 3.0% concordant across all three sources and 5.3% concordant across at least two sources. From 1996 to 2008 the prevalence of diabetes during pregnancy increased from 5.9% (95% CI: 5.6, 6.2) to 10.5% (95% CI: 10.2, 10.8) in NHW women, from 6.4% (95% CI: 6.0, 6.9) to 11.8% (95% CI: 11.4, 12.2) in NHB women and from 4.1% (95% CI: 2.5, 5.7) to 9.3% (95% CI: 8.6, 9.9) in Hispanic women (Figure 1). The prevalence of recognized diabetes is impacted by reporting, screening and diagnostic practices as well as actual changes in disease burden. As the prevalence of diabetes during pregnancy increases it is important to understand its public health impact; not only on the offspring exposed to diabetes *in utero,* but also on the mothers who have either developed frank diabetes at a young age or are at high risk for development of type 2 diabetes.



2430-PO

The Rs12255372 Variant of Transcription Like Factor 7–Like 2 [*TCF7L2*] Is Associated with an Increased Risk of Gestational Diabetes Mellitus in Arab Women

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Genetic and environmental factors are highly interrelated with gestational diabetes mellitus (GDM) and type 2 diabetes (T2D). GDM is a good model for prediction of T2D. To investigate the associations of two variants rs12255372 G/T and rs7903146 C/T of transcription like factor 7–like 2 [TCF7L2] gene with the risk of gestational diabetes mellitus among Arabian population in state of Qatar. A case control study was designed for such genetic association study. A total of 114 unrelated pregnant women (40 gestational diabetes mellitus cases and 74 controls) were recruited from antenatal care unit of Hamad Medical Hospital in Qatar. Study participants were phenotyped by an oral glucose tolerance test. The two variants were genotyped using TaqMan real time PCR assay. The CC, CT and TT genotype frequencies of the rs7903146 variant was not significantly different between the control and GDM cases (39.4%, 50.0%, 10.6% vs. 40.6%, 43.8%, and 15.6%, p=0.444) among Arab subjects, respectively. The GG, GT and TT genotype frequencies of the rs12255372 variant was not significantly different between the control and GDM cases (34.3%, 51.4%, 14.3% vs. 15.6%, 68.8%, and 15.6%, p=0.109) among Arab subjects, respectively. T allele was the minor allele for rs7903146 and its frequency was [0.36] and T allele was the minor allele for rs12255372 with a frequency of [0.43]. All allele frequencies were in equilibrium for HWE among Arab subjects [P=0.706] for rs7903146 and [p=0.108] for rs12255372. Using logistic regression analysis with adjustments of age and body mass index, only the T allele of rs12255372 variant was significantly associated with risk of GDM with odds ratio of 2.370, (95% of CI 1.010-5.563) with the [p= 0.047] among Arab subjects using the genetic dominant model. On the basis of these observations, we can conclude that TCF7L2 rs12255372 variant is associated with an increased risk of gestational diabetes mellitus in Arab pregnant women.

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2431-PO

Utility of an Iterative Intravenous Insulin Infusion Protocol for Glucose Control during Labour in Patients with Diabetes during Pregnancy

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The major determinant of neonatal hypoglycemia is the maternal blood glucose just prior to delivery, hence the importance of maintaining maternal euglycemia during labour. We retrospectively analyzed maternal glucose levels and rates of neonatal hypoglycemia in pregnant women during labour with diabetes, gestational (GDM), type-1 (DM-1) and type-2 (DM-2) managed with an iterative intravenous (IV) insulin and dextrose infusion protocol. IV insulin was routinely planned for women with GDM requiring insulin >0.5 units/kg/day during pregnancy, DM-1 and DM-2. Blood glucose was monitored hourly and the insulin infusion rate adjusted hourly as needed to a target glucose of 4.1–6.0 mmol/L. Patients were included in the review only if protocol was used for at least 6 hours with glucose readings for the 3 hours prior to delivery used for analysis.

A total of 230 delivery records were analyzed, including, GDM (n= 167), DM-1 (n=31) and DM-2 (n=32). The age and body mass index (mean±SD) for GDM, DM-1 and DM-2 was 32.0±5.3, 29.8±5.0, 32.6±6.0 years and 29.0±6.5, 26.7±4.3, 34.0±7.0 kg/M^2 respectively. At birth, the mean insulin dose was 1.0 and 1.3 units per kg per day for DM-1 and DM-2 respectively. The mean gestational age at delivery was 37.0±2.8, 36.7±2.3 and 36.0±4.0 weeks. In the GDM group, 31% were diet controlled, 35% used ≤0.5 units and 34% required >0.5 units/kg/day of insulin. For this abstract, only GDM on >0.5 units/kg/day were analyzed.

Table 1

	GDM		DM-1		DM-2	
IV insulin/Dextrose protocol used for 6h	Yes 22 (39)*	No 35 (61)	Yes 12 (39)	No 19 (61)	Yes 10 (31)	No 22 (69)
Neonatal hypoglycemia (glucose ≤ 2.0 mmol/L)	0 (0)	3 (9)	1 (8)	3 (16)	2 (20)	2 (9)
Maternal hypoglycemia (glucose ≤ 3.5 mmol/L)	1 (4)	4 (11)	2 (16)	4 (21)	0 (0)	0 (0)
Maternal Hyperglycemia (glucose ≥ 7 mmol/L)	1 (4)	4 (11)	1 (8)	3 (16)	0 (0)	9 (41)

* number (%)

These results demonstrate the success of a standardized iterative continuous IV insulin and dextrose infusion protocol in achieving good glycemic control with minimal maternal and neonatal hypoglycemia during labor in women with diabetes.

EPIDEMIOLOGY

2432-PO

60min Post Load Glucose Predicts Future Type 2 Diabetes in Japanese

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The purpose of this study was to determine which time point of plasma glucose during an oral glucose tolerance test (OGTT) best predicted future type 2 diabetes (T2DM). Analyzed subjects included a cohort of 277 nondiabetic Japanese (143 men and 134 women) aged 45 to 74 years. Baseline variables included plasma glucose measured after an overnight fast and at 30, 60 and 120 min during a 75-g OGTT. The OGTT was repeated at follow-up. T2DM diagnosis was based on the American Diabetes Association 1997 criteria. ΔAkaike information criterion (ΔAIC) was used to evaluate which model including fasting plasma glucose (FPG) or 30-, 60-, or 120-min glucose best predicted future T2DM. ΔAIC for T2DM outcome was calculated as the base model including age, gender, and BMI minus the model with FPG or post-load glucose added. ΔAIC ≥2 indicated a meaningful difference in goodness of fit between models. At 5-6 years 65.5% of subjects returned for follow-up and there were 48 (17.3%) cases of incident T2DM. In multiple logistic regression analysis and using a 1-SD increase for continuous variables, 60-min post-load glucose (glucose-60) had a higher odds ratio for future T2DM (5.54; 95% CI, 3.31-9.27) than fasting plasma glucose (FPG) (3.72, 2.51-5.52), 30-min post-load glucose (glucose-30) (4.02, 2.61-6.19) or 120-min post-load glucose (glucose-120) (3.33, 2.22-4.99) after adjusting for age, gender and baseline BMI (the 1 SD values of FPG glucose-30, glucose-60 and glucose-120 were 10.6 mg/dl. 29.5 mg/dl, 48.3 mg/dl and 32.8 mg/dl, respectively). In the receiver operating characteristic (ROC) curve analysis of these multivariate models, the area under the ROC curve of the glucose-60 model (0.866) was greater than that of the FPG model (0.849), glucose-30 model (0.823) or