Welcome to Volume 2 of eDiabetes Review. In this lead-off issue, we review some of the most important new findings presented at the 2015 American Diabetes Association 75th Scientific Sessions (ADA) and the 24th Annual Scientific and Clinical Congress of the American Association of Clinical Endocrinologists (AACE).

As an additional feature, this newsletter issue contains brief interviews with some of the key researchers by eDiabetes Review Program Director, Dr. Kathleen Dungan from The Ohio State University. Links to access both the audio and transcript versions of the interviews are provided.

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Bob Busker
Managing Editor
The Johns Hopkins University School of Medicine eLiterature Review programs.

**LEARNING OBJECTIVES**

After participating in this activity, the participant will demonstrate the ability to describe new findings in:

- Reducing postprandial glycemic variability
- The uses of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors in combination therapy
- The effects of DPP-4 inhibitors on cardiovascular outcomes
- Using diet alone to convert IGT to NGT in prediabetes
- Treatment preferences among patients with type 2 diabetes

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Guest Faculty Disclosure

Kathleen Dungan, MD, MPH has indicated that she has received grant/research funding from AstraZeneca, GlaxoSmithKline, Merck, and Sanofi Aventis. She has served as a consultant for GlaxoSmithKline and has been a paid member of committees, panels, or boards for Eli Lilly and Company, and has received honorarium from UpToDate®.

Andrew Ahmann, MD has indicated that he has received research funding from Novo Nordisk, Inc. and Sanofi. He has served as a consultant for Eli Lilly and Company and Sanofi.

Jennifer Green, MD has indicated that she has received grant/research funding from AstraZeneca, GlaxoSmithKline, Janssen, and Merck. She has served a consultant for Merck.

No other faculty has indicated any financial interests or relationships with a commercial entity.

Unlabeled/Unapproved Uses

The authors have indicated that there will be references to the unlabeled/unapproved uses of saxagliptin (5 mg) and dapagliflozin (10 mg).

Program Directors’ Disclosures
**GLP-1 AGONIST TO REDUCE GLYCEMIC VARIABILITY**


*Presidents Oral Session Abstract from the American Diabetes Association 75th Scientific Sessions; June 5-9, 2015, Boston, Mass.*

Increased variability in blood sugar, and in particular postprandial hyperglycemia, has been associated with systemic inflammation, oxidative stress, and renal/cardiovascular damage. The initial results of a small feasibility study (FLAT-SUGAR [Fluctuation Reduction With Insulin and GLP-1 Added Together]) have revealed that the short-acting GLP-1 agonist exenatide, when taken with meals in patients with type 2 diabetes at risk for cardiovascular events, can reduce glycemic variability compared with basal-bolus insulin, while maintaining similar HbA1c levels. Results were reported at the President's Oral Session during the ADA 2015 Scientific Sessions.

One-hundred-two patients with type 2 diabetes requiring insulin and at high risk of cardiovascular events (32% had had a prior cardiovascular event) were recruited. Patients were given basal-bolus insulin with metformin for an initial run-in stabilization period and then randomized to receive prandial therapy with either the GLP-1 receptor agonist exenatide (Glipulin group) or continuation of rapid-acting insulin analogs (BBI group). At randomization, mean HbA1c for the population was 7.9%. All study participants used continuous glucose monitoring (CGM) throughout the trial — initial coefficient of variation (CV) of glucose was 31.9 ± 6.3% in the Glipulin group vs 30.3 ± 6.2% in the BBI group.

Metabolic markers of cardiovascular risk were assessed at baseline, 13, and 26 weeks in 92 study participants (Glipulin: n = 47; BBI: n = 45). The primary endpoint was change in GV, as assessed by CV using CGM.

Results at week 26 showed no severe hypoglycemia in either group. However, while the HbA1c levels were similar (Glipulin group 7.1 + 0.6% vs BBI group 7.2 + 0.6%), the mean CV CGM was significantly different between the two groups (Glipulin group -2.4 + 7.9% compared to BBI group +0.4 + 5.5% t-test P = 0.047, rank sum: P = 0.024). In addition,
body weight was significantly lower in the Glipulin group at 26 weeks (-4.7 kg vs BBI group +0.8 kg; P < 0.001).

MAGE (mean amplitude of glycemic excursions) was improved in the Glipulin group (rank sum P = 0.049), whereas other markers of GV were not. Biomarker levels for serum amyloid A and alanine aminotransferase were lower in the Glipulin group. No differences were noted in levels of albuminuria, interleukin-6, high sensitivity C-reactive protein, or urinary isoprostanes between the two groups.

The authors believe that the FLAT-SUGAR study results provide evidence meriting further investigation in a larger, multicenter trial to determine whether targeting GV using GLP-1 receptor agonists improves clinical outcomes in diabetes.

**BENEFITS OF ADDING A DPP-4 TO A GLP-1?**

**Presentation Abstract 10-OR:** Adding a DPP-4 Inhibitor to Ongoing Therapy with a GLP-1 Receptor Agonist and Metformin Increases Intact GLP-1, But Does Not Change Insulin or Glucagon Secretion nor Plasma Glucose Excursions following a Mixed Test Meal in Patients with Type-2 Diabetes; Michael A. Nauck, Melanie Kahle, Oleg Baranov, Carolyn F. Deacon, Jens J. Holst. Abstract from the American Diabetes Association 75th Scientific Sessions; June 5-9, 2015, Boston, Mass.

Patients with type-2 diabetes receiving the DPP-4 inhibitor sitagliptin as an addition to their ongoing regimen of metformin plus the GLP-1 receptor agonist liraglutide experienced no added benefits, according to data presented at the ADA 75th Scientific Sessions by Michael A. Nauck MD of St. Josef Hospital in Bochum, Germany.

The 16-patient investigation evaluated five women and 11 men with type 2 diabetes (mean duration of diabetes 9.4 years), with a mean age of 55 years and a mean body mass index of 31.7 kg/m2. HbA1c was 7.5%. Patients were treated with metformin (2044 mg) and liraglutide 1.2 mg daily for at least two weeks, and then randomized to receive either sitagliptin 100 mg or placebo 60 minutes prior to a standard mixed meal. The patients were also studied on two occasions after an overnight fast. The investigation sought to determine whether coadministration of two incretin-based agents would lead to greater glucose-lowering effects.

Glucose excursions served as the primary target outcome. Secondary outcome measures were insulin, C-peptide, glucagon, GLP-1, and total and intact glucose-dependent insulinotropic polypeptide (GIP). ANCOVA was used in the statistical analysis.

The results indicated that sitagliptin increased meal-induced responses of intact GLP-1 by 78.4% and GIP by 90.2% (p< 0.0001). In contrast, total GLP-1 and GIP responses were
nonsignificantly decreased, by 36.5% and 18.2%, respectively. Other results showed that sitagliptin elevated intact incretin plasma concentrations after a standard mixed meal, but appeared to have an insignificant effect on insulin, C-peptide, glucagon and glucose concentrations (P = 0.60-1.00). The influence of sitagliptin treatment on incretin plasma concentrations was similar to previous results in patients with type 2 diabetes on metformin treatment alone.

Dr. Nauck explained that GLP-1 receptor agonists and DPP-4 inhibitors are both incretin-based drugs that are thought to exert their glucose-lowering activity by stimulating GLP-1 receptors. “GLP-1 receptors are most likely to be maximally stimulated by liraglutide alone,” according to Dr. Nauck.

These study results, therefore, do not support the use of a GLP-1 receptor agonist and a DPP-4 inhibitor in combination, the researchers say.

Commentary from Program Director Dr. Kathleen Dungan:
These data demonstrate that the additional endogenous GLP-1 levels mediated by DPP-4 inhibition did not give rise to a postmeal clinically meaningful change in glucose. This may be a result of near-maximal stimulation of GLP-1 receptors by liraglutide alone. The study also suggests that augmentation of other incretins which are substrates for the DPP-4 enzyme play a minimal role in the glucose lowering effect of DPP-4 inhibitors.

EFFECT OF SITAGLIPTIN ON CARDIOVASCULAR OUTCOMES

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes; The TECOS Study Group. Presented at the American Diabetes Association 75th Scientific Sessions; June 5-9, 2015, Boston, Mass.

Emerging data from the TECOS trial asserted the cardiovascular safety of the DPP-4 inhibitor sitagliptin in patients with type 2 diabetes who had established cardiovascular disease. This large-scale randomized double-blind cardiovascular outcomes study compared 14,671 patients with type 2 diabetes and cardiovascular disease to either sitagliptin (n=7332) or placebo (n=7339) in addition to their existing therapy. Results were presented at the ADA 75th Scientific Sessions.

At initiation, the baseline mean HbA1c was 7.2% (6.5 to 8.0%), and the patients had been living with diabetes for a mean 11.6 years. The primary composite cardiovascular outcome was defined as the first confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. The secondary composite cardiovascular outcome was the first confirmed event of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

During a median follow-up of three years, TECOS researchers noted that, overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6% 4.17 per 100 person-years). Sitagliptin was found to be noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, range: 0.88 to 1.09; P < .001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, range: 0.83 to 1.20; P = .98), as has been suggested in trials of other DPP-4 inhibitors, according to TECOS researchers.

The study reported a small difference in HbA1c levels (least-squares mean difference for sitagliptin vs placebo, - 0.29 percentage points; 95% CI, range: - 0.32 to - 0.27). There was no significant increase in the rate of severe hypoglycemia among patients in the sitagliptin group compared with the placebo group, and fewer patients in the sitagliptin group required additional antihyperglycemic agents or started long-term insulin therapy during the study period.
While concerns have been raised about a possible association between incretin-based therapies and adverse pancreatic effects, acute pancreatitis was uncommon in TECOS trial patients; although it occurred more often in the sitagliptin group, the difference was not significant. Furthermore, there were no significant between-group differences in rates of acute pancreatitis (P = .07) or pancreatic cancer (P = .32).

The observation that sitagliptin therapy was not associated with a change in long-term rates of cardiovascular events is consistent with the findings from shorter-term outcome trials of other DPP-4 inhibitors, including saxagliptin (SAVOR-TIMI 53) and alogliptin (EXAMINE). However, the outcomes of the SAVOR-TIMI 53 trial revealed an unexpected excess rate of hospitalization for heart failure in patients receiving saxagliptin compared to those receiving placebo, and the EXAMINE trial showed a nonsignificant numerical imbalance in hospitalization for heart failure in the alogliptin group. In contrast, TECOS, a larger study group with a longer follow-up period, found that rates of hospitalization for heart failure did not differ between the sitagliptin and placebo groups.

The study results showed that sitagliptin may be used in a diverse group of patients with type 2 diabetes who are at high cardiovascular risk without increasing rates of cardiovascular complications; however, these results cannot exclude possible benefits or risks with longer durations of therapy or in patients with more complicated coexisting illnesses.
DPP-4 inhibitors and the newer sodium-glucose linked transporter-2 (SGLT-2) inhibitors have complimentary mechanisms of action that, at least theoretically, present the potential to improve glucose control in patients with type 2 diabetes without increasing the risk of hypoglycemia. Several interesting studies, presented at the ADA 75th Scientific Sessions and/or at the 24th Annual Scientific and Clinical Congress of the American Association of Clinical Endocrinologists (AACE), reported on investigations into treatment approaches combining these two agent classes.

ADA Presentation Abstract 105-OR: One investigation added dapagliflozin to a regimen of saxagliptin plus metformin. The study involved an open-label lead-in period in which patients on metformin (baseline HbA1c 8.0%–11.5%) received open-label saxagliptin 5 mg and metformin for 16 weeks, while patients on metformin and any DPP-4 inhibitor (baseline HbA1c 7.5%–10.5%) received open-label saxagliptin 5 mg and metformin for 8 weeks. At the end of the lead-in period, 320 patients with inadequate glycemic control (HbA1c 7%-10.5%) were then randomized to receive either placebo or dapagliflozin 10 mg while continuing open-label saxagliptin and metformin.

The study met its primary endpoint: at 24 weeks, the triple drug combination (dapagliflozin 10 mg/saxagliptin 5 mg plus metformin) achieved significantly greater mean reductions in HbA1c compared placebo (-0.82% versus -0.10%, respectively; P < .0001). Secondary endpoint outcomes indicated that more patients in the dapagliflozin combination group achieved A1c < 7% compared to placebo (38% vs 12%, respectively, P < .0001), as well as greater reductions in fasting plasma glucose, 2-hour postprandial glucose, and weight compared to patients receiving placebo. The regimen was well tolerated, with no major hypoglycemic episodes, and a similar incidence of urinary tract infections in both groups (5% in the dapagliflozin group vs 6.3% in the placebo group).

ADA Presentation Abstract 104-OR: A similar investigation into triple (SGLT-2, DPP-4, metformin) therapy trialed saxagliptin as the add-on therapy. Patients with type 2 diabetes who had a baseline HbA1c of 8.0%-11.5% (mean 9.3%), on stable metformin therapy (≥1500 mg/d) for at least eight weeks, received open-label dapagliflozin 10 mg/d with metformin for 16 weeks. Patients with inadequate glycemic control (A1c 7%-10.5%) were then randomized to either saxagliptin 5 mg/d triple therapy (n = 162) or placebo (n = 153). The primary end point was change in A1c from baseline to week 24, with secondary end points including fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG), and the proportion of patients achieving A1c < 7%.

The investigators reported a significantly greater A1c reduction at 24 weeks (-0.51 vs. -0.16% in the saxagliptin and placebo group respectively, P < .0001) with the addition of dapagliflozin (triple combination therapy), with a greater proportion of patients reducing A1C to below 7% (35% vs. 23%, P = 0.007). Reductions in FPG and PPG were similar between treatment arms. Episodes of hypoglycemia were rare, and adverse events were similar across treatment groups, although urinary tract infections and nasopharyngitis were more common in the triple therapy group.

AACE Abstract 1213: Patients with type 1 diabetes were the focus of a retrospective analysis that studied 10 patients (baseline A1c: 8.01 ± 0.22%) under treatment with insulin (0.7 ± 0.1 u/kg daily) and receiving liraglutide for 11 ± 2 months. Dapagliflozin was added, starting at a dose of 5 mg daily and increased to 10 mg daily one week later.

At the end of 12 weeks of this triple-therapy regimen, although total insulin dose remained unchanged, mean A1c fell by 0.66 ± 0.22% (P = .0004) and mean glucose fell by 28 ± 2 mg/dL from a baseline level of 172 ± 9 mg/dL (P = .016). No additional hypoglycemia was observed, and benefits were seen in body weight and blood pressure.

Commentary from Program Director Dr. Kathleen Dungan:
These data demonstrate the possibilities of expanded use of SGLT-2 inhibitors. The first two abstracts demonstrate the efficacy of triple therapy using metformin and either SGLT2 inhibitor or DPP-4 inhibitor followed by the remaining class in patients who did not achieve glycemic control with the first add-on therapy. The results demonstrate strong HbA1c lowering effects when the SGLT-2 inhibitor is added to metformin plus DPP-4 inhibitor and significant though less pronounced HbA1c reduction when a DPP-4 inhibitor is added to SGLT-2 inhibitor. In both cases, the absolute reduction in HbA1c may be less pronounced than that observed with monotherapy or as a single agent add-on to metformin. This is
consistent with known strategies for combining glucose lowering therapies. Comparisons of these studies should be performed with caution, however, because of slightly different enrollment criteria and because selection for failure of one agent may have a differential impact on efficacy of subsequent therapies. The use of SGLT-2 inhibitors and liraglutide are novel strategies that are currently under investigation for type 1 diabetes. The initial data are promising, particularly in light of their weight-sparing effects, as obesity and weight gain are prevalent in patients with type 1 diabetes. However, further evidence of safety are needed, particularly in light of recent reports of diabetic ketoacidosis associated with SGLT-2 inhibitors. The data emphasize the importance of insulin as primary therapy.

EFFECT OF DIET IN PREDIABETES

Presentation Abstract 90-OR: Remission of impaired Glucose Tolerance (IGT) to Normal Glucose Tolerance (NGT) in Obese Adults with High Protein vs. High Carbohydrate Diet; Abbas E. Kitanchi, Amy Brewer, Jim Wan, Chirs Sands, Frankie B. Stentz. Abstract from the American Diabetes Association 75th Scientific Sessions; June 5-9, 2015, Boston, Mass.

In patients with prediabetes who are obese, can diet alone achieve remission of impaired glucose tolerance (IGT)? Research comparing a high-protein vs a high-carbohydrate diet provide evidences that the former may be more effective in attaining normal glucose tolerance (NGT).

In this study, 18 obese patients with prediabetes were randomized to either a high-protein (HP) diet (30% protein, 30% fat, 40% carbohydrates) or a high-carbohydrate diet (HC) diet (15% protein, 30% fat, 55% carbohydrates) for six months. All food was provided. Baselines were established with Oral Glucose Tolerance Tests (2 hour glucose between 140 – 199 mg/dl defined as IGT), dual x-ray absorptiometry (DXA) to estimate fat-free mass, and HOMA-IR (homeostasis model assessment-estimated insulin resistance).

At six months, the HC group had experienced greater weight loss. But in the HP group, lean body mass increased (+2.8 ± 0.4%) while it decreased in the HC group (-2.1 ± 1.1%). Fat mass decreased in both groups, by 2.5 ± 0.4% in the HP group and 3.5 ± 0.9% in the HC group. Other changes from baseline included:

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<th>HP Baseline</th>
<th>Change</th>
<th>HC Baseline</th>
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<tr>
<td>Insulin Resistance</td>
<td>4.69 ± 0.26</td>
<td>1.58 ± 0.14</td>
<td>4.62 ± 0.26</td>
<td>3.15 ± 0.27</td>
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<td>HbA1c</td>
<td>5.99 ± 0.05</td>
<td>5.53 ± 0.02</td>
<td>5.9 ± 0.04</td>
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Most importantly, conversion to normal glucose tolerance was 100% (9/9) in the HP diet group versus 44.4% (4/9) in the HC. These results suggest that lean body mass preservation may be more important than total weight loss in the conversion of IGT to NGT, possibly due to the high insulin sensitivity of muscle cells.

Click here to hear eDiabetes Review Program Director Dr. Kathleen Dungan discuss "Diet and Remission of Impaired Glucose Tolerance" with study author Dr. Frankie B. Stentz
UNDERSTANDING PATIENT TREATMENT PREFERENCES

Presentation Abstract 206-OR: Most Influential Factors Determining Patient Preferences for Type 2 Diabetes Treatment; Kelly Bell, Emuella M Flood, France Ginchereau-Sowell, Marie Delacruz. Abstract from the American Diabetes Association 75th Scientific Sessions; June 5-9, 2015, Boston, Mass.

To successfully implement true patient-centered care, clinicians need to understand and address each individual patient's treatment preferences, challenges, and barriers. The results of this study, identifying the most influential attributes of diabetes treatment from the patient perspective, provide valuable information to assist clinicians in developing a shared decision-making approach.

Adults with type 2 diabetes living in the US were recruited through a market research panel and asked to complete an on-line, adaptive, conjoint survey that was customized to each respondent. Attributes included treatment efficacy as measured by the improvement in HbA1c, the risk of twelve different adverse events, and dosing convenience as described by dosing mode and timing. Respondents chose between hypothetical treatments with different attributes. Using Sawtooth Software, ordinary least-squares and hierarchical Bayes regression were used to calculate utilities and attribute importance ratings.

One hundred-sixty-seven eligible respondents completed the survey and were included in the analysis. The mean participant age was 58 years (SD 11.6), 55% were female, 84% were white, and 57% had a college degree or higher. Among the findings:

• The most influential treatment attribute was convenience (dosing mode and timing) with the highest mean importance rating (10.51%) relative to other attributes, and the highest percentage of patients considering it most important (35.3%).
• The risk of diarrhea: 10.42% importance rating, with 22% rating it most important;
• Weight change: 9.96% importance rating, with 16% rating it most important;
• Risk of hypoglycemia: 9.29% importance rating, with 8% rating it most important;
• Treatment efficacy: 9.08% importance rating, with 15% rating it most important;
• Serious but rare adverse events were deemed less important.

These findings clearly indicate that patients' treatment preferences revolve primarily around convenience; ie, a lesser potential for impact on their everyday function and routine, and should help guide clinicians in implementing patient-centered care achieve improved outcomes.

Commentary from Program Director Dr. Kathleen Dungan:

The results of this study demonstrate clearly that patient treatment preferences may differ substantially from those of their providers. Patients consider convenience most influential, while providers are typically most concerned with efficacy and safety. These treatment preferences may partly explain the gap in outcomes observed from clinical trials compared to real world experiences, in that preferences are likely to affect adherence to medication. Adherence to medication is a prerequisite for successful response to therapy. Of note, cost is another important treatment consideration that was not reported in this analysis. The study highlights the need for continued research in real-world outcomes studies. In the absence of compelling data directing choice of therapy, patient preferences should be considered.
IMPORTANT CME/CE INFORMATION

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