2016 ADA AND AACE CONFERENCE HIGHLIGHTS

In this Issue...

In this issue, we cover presentations given at the 2016 American Diabetes Association 76th Scientific Sessions (ADA) and the 25th Annual Scientific and Clinical Congress of the American Association of Clinical Endocrinologists (AACE). These meetings offer a unique forum for discussion and learning, which ensures that international expertise is shared by diabetes specialists from all over the world.

Here, we highlight reports that address improvements in glycemic management, such as the efficacy of once-weekly exenatide on glucose fluctuation, a study on the rate of hypoglycemic events in patients taking insulin in combination with different agents, and the safety and efficacy achieved with MK-1293, an investigational insulin glargine. Other topics of interest include adjustments in insulin dosages for post-bariatric surgical T2D patients, a guide to weight-loss medications for obese patients with kidney and cardiovascular diseases, and the implementation of point-of-care testing (POCT) and POCT hospital connectivity for seamless diabetes management.

LEARNING OBJECTIVES

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

- Discuss glycemic fluctuations in T2D patients with once-weekly exenatide.
- Describe differences in the rates of documented hypoglycemia events with insulin.
- Identify a new investigational insulin glargine to treat T2D.
- Discuss ways to treat multimorbid obese patients with the appropriate weight loss meds.
- Describe the advantages of automated integration of POCT glucose results for hospitalized adults with diabetes.
- Identify appropriate new insulin dosage for post-bariatric surgical T2D patients.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

GUEST AUTHORS OF THE MONTH

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Guest Faculty Disclosure
Nestoras Mathioudakis, MD has indicated that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of
Stephanie Petrou Binder, MD has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

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 MK-1293.

**Program Directors' Disclosures**

**INTERVIEWS**

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**INTERVIEW DISCLOSURES**

Dr. Reddy has disclosed that he has served as an advisor for Calibra and Janssen, a speaker and an advisor for Merck, and an investigator for PCORI and Lexicon.

Dr. Mechanick has indicated that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

Dr. Rendell has disclosed that he has received grant and research funding from AstraZeneca, Boehringer Ingelheim, and Eli Lilly and Company, GlaxoSmithKline, Hanmi, Intarcia Therapeutics, Merck & Co., Inc., Pfizer and Co., and Sanofi.

**IMPG**

Inpatient Glycemic Management: From the Beside to the Cloud. Sethu Reddy.

The challenge and complexity of care in persons hospitalized with hyperglycemia and the limited guidance in the area of in-patient glycemic management (IPGM) has forged
the way for an evolving patient management protocol that begins at the bedside and ends in the cloud.

Physicians at the Cleveland Clinic discussed the advantages of instituting formal glycemic management teams in hospitals, the integration of electronic medical records (EMR) with glucometric data, and the use of remote automated laboratory systems (RALS) for improved diabetes management and the immediate archiving and availability of patient facts and statistics, in a presentation given at the AACE 25th Annual Scientific and Clinical Congress.

According to the presentation, improvements in the treatment of hospitalized hyperglycemic individuals, as well as how well these patients fare once discharged from hospital, need to come from many different angles that include better nurse management protocols, improved patient self-management, point of care testing (POCT), real-time continuous glucose monitoring (CGM), and hospital POCT connectivity.

Based on the nurse education and transition (NEAT) model, hospitalized patients with diabetes require a thorough education before being allowed to leave supervised care, to reinforce their "survival skills" once on their own again. NEAT key elements include brief educational videos focused on diabetes self-management skills like nutrition, medication-taking, insulin injections, blood glucose monitoring, and hypoglycemia. With the development of nurse "cheat sheets" to aid in patient knowledge acquisition, survival skills take-home sheets, diabetes education resource lists to aid in scheduling outpatient visits prior to discharge, and uniform documentation guidance in electronic medical records, NEAT aims to reduce the likelihood of rehospitalization and ICU admission of posthospitalized diabetic patients.

A new direction in IPGM suggests that point-of-care testing – diagnostic laboratory testing carried out at or near the bedside – can be an advantage in situations requiring quick decision-making based on imminent test results. The challenges of POCT are largely related to quality assurance, as POCT is performed by members of the clinical staff and not laboratory-trained individuals. POCT is also more expensive than lab testing. The advantages, however, outweigh these challenges, as improved communication can lead to improved glucose regulation and increased safety. POCT results feed into the patient EMR and may result in more accurate glucose results, since transcription errors by nurses may result in inaccurate documentation of glucose values and times. Such errors have the potential to result in incorrect insulin doses, which has obvious patient safety implications.

Obstacles to POCT connectivity include privacy and ownership, need for smarter algorithms, data analysis for just-in-time expert advice, and need for new players such as Google, Verizon, or Apple, for instance, for smooth functionality. The benefits of POCT connectivity include patient identification, operator identification, data management, and live-data intervention.

Clinicians believe that POCT connectivity provides the enormous advantage of access to all of an individual patient's testing history and trends, even if the patient moves to a different facility or is discharged. It allows real-time analysis, helps reduce medical errors, and eliminates transcription errors. Most important, POCT connectivity benefits the patient by allowing the physician to enter and retrieve data on diabetic patients for the better management of hypo- and hyperglycemia.
Almost 90% of people with type 2 diabetes are overweight or obese. The impact of diabetes on the body is widespread, affecting various organ systems in the form of blindness, end-stage kidney disease, nontraumatic lower extremity amputations, cardiovascular complications, and strokes.

Even among young people, obesity and diabetes are growing health problems that need to be taken seriously by health care practitioners. This was the subject of a report presented at the AACE's 25th Annual Scientific and Clinical Congress from the Icahn School of Medicine at Mount Sinai, which highlighted the necessity of obesity reduction and recommended a highly individualized, patient-centered care approach.

The problem in treating overweight and obesity is the lack of a structured care system that offers obesity guidelines and individualized, patient-centered obesity care, and that incorporates lifestyle, pharmacotherapy, and therapeutic procedures. Health care organizations need to facilitate the work of high-performing, patient-centered teams to achieve safe, effective, timely, and equitable care for obese persons.

Researchers believe that greater weight loss and weight loss maintenance can be achieved through the addition of pharmacotherapy than with lifestyle therapy alone and should be offered to patients with obesity when the potential benefits outweigh the risks for the chronic treatment of their disease.

Individualized pharmacotherapy is integral to patient-centered care. It involves clinical decision-making that takes a person's comorbidities into account. Not all medications are suitable for multimorbid patients, however, as the obesity guide shows.

In selecting the optimal weight loss medication for each patient, clinicians should consider differences in efficacy and side effects of obesity medications, as well as the presence of weight-related complications and medical history – these factors are the basis for individualized weight loss pharmacotherapy.

In chronic kidney disease, all weight loss medications can be used with appropriate caution in patients with mild (creatinine clearance 50 mL/min-79 mL/min) and moderate (30 mL/min-49 mL/min) renal impairment. These include naltrexone ER/bupropion ER, lorcaserin, or phentermine/topiramate ER, orlistat, and liraglutide 3 mg, with caution to medication choice for patients with severe renal impairment and end-stage renal failure. Persons with nephrolithiasis best respond to treatment with naltrexone ER/bupropion ER, lorcaserin, and liraglutide 3.0 mg.

In patients with existing hypertension, orlistat, lorcaserin, phentermine/topiramate ER, and liraglutide 3 mg are the preferred weight-loss medications. Heart rate should be carefully monitored in patients receiving liraglutide 3 mg and phentermine/topiramate ER. Naltrexone ER/bupropion ER should preferably be avoided.

Obesity in persons with established atherosclerotic cardiovascular disease should be treated with orlistat and lorcaserin. Liraglutide 3 mg, phentermine/topiramate ER, and naltrexone ER/bupropion ER are reasonable to use with caution, and to continue using if weight-loss goals are met, with careful monitoring of heart rate and blood pressure.

Elderly patients should be selected for weight-loss therapy involving structured lifestyle interventions that include reduced-calorie meal plans and exercise, with clear health-related goals in mind that include prevention of T2D in high risk patients with prediabetes, blood pressure lowering, and improvements in osteoarthritis, mobility, and physical function.

Patients who have undergone bariatric surgery require an extensive lifestyle intervention that need not include weight-loss medication. Patients who have regained excess weight (≥ 25% of the lost weight), who have not responded to intensive lifestyle intervention, and...
are not candidates for reoperation may be considered for treatment with liraglutide 1.8 mg-3.0 mg or phentermine/topirimate ER.

Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone. In addition to improving glycemic control, weight loss is a huge step toward overall health, as well as helping control diabetes.

Click here to hear eDiabetes Review Program Director Dr. Nestoras Mathioudakis discuss A Patient-Centered Approach for Individualization of Pharmacotherapy in Obesity Care with Dr. Jeffrey Mechanick

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INSULIN AFTER BARIATRIC SURGERY


A five-year retrospective study that investigated the insulin requirements of type 2 diabetes (T2D) patients immediately following bariatric surgery demonstrated that Roux-en-Y gastric bypass surgery greatly improved glycemic control in persons with T2D, indicating an 86% reduction in the total daily insulin dose on the second post-operative day.

The study investigators from the Cleveland Clinic's STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial presented their data at the AACE 25th Annual Scientific and Clinical Congress. The study compared baseline and postsurgical insulin dosage requirements and determined perioperative glycemic measures in T2D patients who received bariatric surgery in their clinic between 2010 and 2014.

The retrospective chart review included 114 bariatric patients who were 55% female and 75% Caucasian, with a mean age of 52.8 years. Their mean BMI was 46.2 kg/m2 and mean hemoglobin A1c was 8.3%. Seventy-nine percent of the patients had hypertension, 82% had lipid disorders, and 66% were on insulin plus noninsulin medications, with the remainder (34%) on insulin only.

The study compared BG levels and insulin doses of patients prior to admission (Baseline), on the day of surgery (DOS), and postoperative days 1 and 2 (POD1, POD2), using a paired t-test. Subgroup analyses were performed on patients who demonstrated blood glucose (BG) 100 mg/dL-140 mg/dL more than 50% of the time on POD2, while t-test comparisons were done in patients with poorer BG control.

The study data was as follows: mean BG levels were 185 ± 43 mg/dL on DOS, 171 ± 41 mg/dL on POD1 (P < .0001 vs DOS), and 160 ± 36 mg/dL on POD2 (P < .0001 vs DOS).

The mean daily insulin dose was 85.8 ± 62.9 units at Baseline, 11.5 ± 13.2 units on DOS, 16.8 ± 21.2 units on POD1, and 11.5 ± 15.3 units on POD2, with P < .0001 for all time points vs Baseline.

Among the subgroup of subjects with good control, the A1c was 7.9% ± 1.6. The mean
Daily insulin dose in this subgroup was 75.6 ± 55.7 units at Baseline, 7.7 ± 7.6 units on DOS, 8.7 ± 11.6 units on POD1, and 4.0 ± 6.2 units on POD2, all with P < .0001 vs Baseline.

On POD2, 95% of patients were on insulin only, which was consistent with recommendations for inpatient T2D treatment, while the rest of the patients were on insulin plus noninsulin medications. Glycemic control on POD1 and POD2 was fair, falling in the upper end of the ADA guidelines of 100 mg/dL-180 mg/dL in hospitalized patients.

Mean BG levels were 160 mg/dL-170 mg/dl on 0.09 units/kg -0.13 units/kg of insulin, corresponding to an 86% reduction, on POD1 and POD2, when patients received a clear liquid diet every hour. This assessment could be useful in developing algorithms for insulin titration after bariatric surgery, according to the investigators.

The group as a whole had an 86% reduction in the total daily dose of insulin by POD2. This reduction was 95% in the subgroup with good glycemic control, despite lower BGs. While patients with type 2 diabetes may be expected to require as much as 50% less insulin while receiving an NPO or clear liquid diet, the 86% reduction in total daily insulin doses suggests the reduced insulin requirements are also due to immediate hormonal changes due to bariatric surgery.

MK-1293


In results presented at the 76th Scientific Sessions of the ADA from a phase 3 study evaluating MK-1293, an investigational insulin glargine for treatment in persons with type 2 diabetes (T2D), the drug achieved its primary safety and efficacy endpoints by demonstrating noninferiority in A1c change from baseline and matched the safety results of originator insulin glargine (Lantus) after 24 weeks.

The investigation also achieved its secondary endpoint of statistical A1c equivalence to Lantus, demonstrating that treatment with the investigational agent MK-1293 is similar, within an acceptable range, to originator insulin glargine, a commonly used medication for patients with T2D.

MK-1293 is a biosimilar insulin glargine under development that uses Lantus as the originator benchmark. Insulin glargine is an injected, long-acting insulin analogue whose effect lasts evenly for roughly 24 hours.

The phase 3, randomized, active-controlled, open-label, 52-week trial enrolled 531 T2D patients whose diabetes was inadequately controlled by diet and exercise alone. They were randomized 1:1 to receive either once daily MK-1293 (n = 265) or Lantus (n = 266).

The primary efficacy objective was noninferiority of change from baseline A1c at week 24. At baseline, the patients had an A1c level of equal to or less than 11% and were eligible for (or were taking) basal insulin greater than or equal to 10 U/day.

The study demonstrated MK-1293 noninferiority to Lantus, thereby meeting its primary endpoint. The least-squares mean difference in A1c (MK-1293 minus Lantus) was 0.03% (95% CI: - 0.12, 0.18), meeting A1c inferiority (upper bound of the confidence interval less than 0.4%) and equivalence (confidence interval within - 0.4% and 0.4%) criteria. Both study groups had similar basal insulin doses, with an MK-1293 minus Lantus difference of 1.4 U/day (95% CI: - 2.2, 4.9 U/day).

The primary safety objective was antiinsulin antibody (AIA) development. Similar AIA, including incidence and titers, and similar neutralizing antibody responses were seen between the treatment groups.

In the study, 29.0% of patients taking Lantus and 34.7% taking MK-1293, irrespective of AIA status at baseline, had an AIA positive at or before week 24. Additionally, 14.9% of patients treated with Lantus and 19.3% of patients receiving MK-1293 who were
negative of AIA at baseline had an AIA positive at or before week 24.

The study did not identify clinically meaningful between-group differences for predefined safety endpoints of interest, such as hypoglycemia, injection site reaction, systemic allergic reactions, angioedema, and severe cutaneous adverse reactions. Symptomatic hypoglycemia was observed in 52.1% of patients receiving Lantus and 53.2% of patients receiving MK-1293. Lantus patients had injection site reactions in 0.4%, while this was seen in 1.9% of MK-1293 patients. Systemic allergic reactions and anaphylaxis were both noted in 0.4% of the MK-1293 patients and in none of the Lantus patients. Finally, 1.1% of patients receiving Lantus and 0.4% of patients receiving MK-1293 experienced angioedema or a severe cutaneous adverse reaction.

In summary, MK-1293 demonstrated similar efficacy and safety to Lantus in T2D patients receiving the medication for over 24 weeks. Biosimilar insulins are likely to continue to emerge in the coming years as commercial insulins go off patent. These biosimilar medications have different FDA regulatory pathways, which may enable more rapid time to market, and they have the potential to reduce costs for patients.

Click here to hear eDiabetes Review Program Director Dr. Nestoras Mathioudakis discuss Efficacy and Safety of MK-1293 Insulin Glargine Compared with Originator Insulin Glargine (Lantus) in Type 2 Diabetes (T2D) with Dr. Marc Rendell

Click here to access the transcript version of the interview

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HYPOGLYCEMIC EPISODES HIGHEST WITH INSULIN MONOTHERAPY


Hypoglycemia, or low blood glucose, is the critical limiting factor in the glycemic management of patients with diabetes. The goal of glycemic management is to achieve consistent, long-term euglycemia, as glucose instability not only leads to acute hypoglycemic episodes but may also contribute to the development of long-term systemic complications.

A new study presented at the 76th Scientific Sessions of the ADA revealed that documented hypoglycemia in adult-onset, type 2 diabetes (T2D) patients treated with insulin was seen more frequently among patients treated with insulin alone or insulin plus sulfonylurea than in patients treated with insulin plus other antihyperglycemic agents.

The retrospective database analysis using the 2013 MarketScan database was conducted among T2D patients between the ages of 18 to 65 years on insulin therapy who had one or more pharmacy claims.

The index date was defined as the dispensing date of the first antihyperglycemic agent (in 2013). Documented hypoglycemia events were evaluated from the index date to December 31, 2013 or until the end of enrollment, whichever came first, based on medical claims using a validated coding algorithm.
The objective of the study was to estimate the frequency of documented hypoglycemia requiring either hospitalization or emergency room visits among T2D patients treated with insulin. The rates of documented hypoglycemia were calculated for all eligible patients and by treatment subgroups, including insulin, insulin plus sulfonylurea, and insulin plus other antihyperglycemic agents.

The analysis included a total of 141,659 T2D patients from the database who had undergone insulin treatment in 2013. The mean patient age was 53 years and the patients were 53.1% male. The median follow-up was 10.8 months.

The overall rate of documented hypoglycemia requiring hospitalization or emergency room visits among all insulin users was 3.21% (95% CI: 3.11 - 3.32), however, there were differences in the rate of documented hypoglycemia, depending on which agent was taken together with insulin, or for insulin users alone.

Among the 113,574 persons whose treatment consisted of insulin alone, the rate of documented hypoglycemia was 3.49% (95% CI: 3.37 - 3.61). The mean age in this group was 53.1 years, and they were 53.1% male.

Persons taking insulin plus sulfonylurea agents (n = 6,528) were documented to have hypoglycemia at a rate of 2.90% (95% CI: 2.47­3.40). Their mean age was 53.2 years and 55.3% were male.

For persons taking insulin with antihyperglycemic agents other than sulfonylureas, the rate of documented hypoglycemia was 1.79% (95% CI: 1.60 - 2.00). The mean age in this group was 52.2 years, and they were 52.5% male.

Insulin and sulfonylureas are antidiabetic drugs widely used in the management of T2D. They may induce hypoglycemia due to increases in exogenous or endogenous insulin levels, which can occur if the dose is too high or in association with inadequate carbohydrate intake. Hypoglycemia is the most common side effect of the sulfonylurea agents, which can limit their use in select populations at higher risk for hypoglycemia (eg, renal disease).

The study concluded that the likelihood of an emergency hypoglycemic event varied among insulin-treated patients with diabetes. Such events were more common among patients treated with insulin alone or insulin plus a sulfonylurea compared to patients who took insulin together with other antihyperglycemic agents. Patients treated with insulin and sulfonylureas should be informed about risk of hypoglycemia and have a good understanding of how to correct hypoglycemia should it develop. Glucagon emergency kits should be considered for insulin-treated patients, particularly those on a multidose injection regimen.

EXENATIDE QW STEADIES GLYCEMIC INSTABILITY


Patients with type 2 diabetes (T2D) need to gain even control over the degree of their glucose swings, as glucose instability can contribute to the development of micro- and macro-vascular complications.

A new study presented at the 76th Scientific Sessions of the ADA found that the glucagon-like peptide-1 agonist (GLP-1), exenatide, once weekly (QW), was well tolerated in patients with T2D and led to improved glycemic control as early as study week 4. Reductions were observed in 24-h mean weighted glucose, mean amplitude of glucose excursions (MAGE), postprandial blood glucose (PPG), fasting plasma glucose (FPG), and time in the hyperglycemic range, without increasing the risk of hypoglycemia or unexpected adverse events. Glycemic control was consistent through week 10 as shown by 24h glucose.

The objective of this randomized, controlled, double-blind, phase 4 clinical study was to compare glycemic variability in T2D patients receiving exenatide QW to a matched
placebo (PBO) group that had been previously treated with and inadequately controlled on metformin (MET) therapy, based on the 24h glucose profile obtained from continuous glucose monitoring (CGM).

The patients were randomized 1:1 to exenatide QW 2 mg or PBO for 10 wks. Glucose concentration was measured over 7 days at baseline and on study weeks 4 and 10 using the CGM system, Dexcom G4.

At baseline, hemoglobin A1c was 8.2% in the exenatide QW group (n = 60) and 8.0% in the PBO group (n = 56). The 2h PPG was 221 mg/dL in both groups and FPG was 178 mg/dL in exenatide patients and 168 mg/dL in PBO patients.

The study met its primary endpoint: compared with PBO, exenatide QW significantly (P < .001) reduced 24h mean weighted glucose from baseline to week 4 (EQW: -26.0 ± 3.6 mg/dL vs PBO: -5.3 ± 3.9 mg/dL; difference: -20.8 ± 5.3 mg/dL) and to week 10 (-30.8 ± 4.5 mg/dL vs -3.0 ± 4.8 mg/dL; difference: -27. ± 6.6 mg/dL).

Significantly greater reductions were also observed with exenatide QW in 2h PPG (P < .001) at week 4 (EQW: -32 mg/dL vs PBO: -2 mg/dL; difference: -30 mg/dL), and increasingly at week 10 (-44 mg/dL vs -6 mg/dL; difference -38 mg/dL). FPG reductions were significantly (P < .001) greater with exenatide QW vs PBO at week 4 (EQW: -30 mg/dL vs PBO: -2 mg/dL; difference: -28 mg/dL) and at week 10 (EQW: -39 mg/dL vs PBO: -5 mg/dL; difference: -34 mg/dL). Exenatide QW patients also showed a significantly (P < .001) greater reduction of -18 mg/dL in MAGE compared to PBO patients at week 10.

Time in the euglycemic range in the exenatide QW vs PBO groups was 53% vs 55% at baseline, 71% vs 60% at Week 4, and 77% vs 58% at Week 10. Time in hyperglycemic range in the exenatide QW vs PBO groups was 47% compared to 45% at baseline, 29% compared to 40% at week 4, and 22% compared to 42% at week 10. Time in hypoglycemic range for exenatide QW vs PBO was 0.1% vs 0.1% at baseline, 0.6% vs 0.3% at week 4, and 0.7% vs 0.3% at week 10.

Excessive glycemic fluctuations, characterized by exaggerated PPG excursions and hypoglycemia, may provide important data to consider, in addition to A1c, when treating patients with T2D. By virtue of their dosing frequency, once-weekly formulations of GLP-1 agonists are an attractive option in type 2 diabetes management, since they produce significant reductions in glycemic control while promoting weight loss.
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