Highlights from the 76th Annual Scientific Sessions of the American Diabetes Association

June 10 - 14, 2016
New Orleans, LA

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Dear Colleague:

Time restraints prevented many of you from attending the 76th Annual Scientific Sessions of the American Diabetes Association (ADA) which was held a few weeks ago in New Orleans, LA. Therefore, we developed Diabetes 2016 so that important information presented at the Conference could be shared with you on a timely basis.

Diabetes 2016, a newsletter CME program, is being offered to you by Yale School of Medicine with the support of educational grants from Eli Lilly and Company, Merck & Co., Inc., and also supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc., which was made possible, in part, through a collaboration with Eli Lilly and Company. This booklet contains four Diabetes 2016 newsletters and a post-test. After successfully completing the test online you will qualify for a maximum of 5.0 AMA PRA Category 1 Credits™ to be issued by Yale School of Medicine. Term of approval: June 2016 to December 31, 2016.

After successfully completing the program, you will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, inflammation, and atherosclerosis in patients with Type 2 diabetes.
- Underscore the importance of lifestyle change, exercise, and dietary interventions in the management of diabetes.
- Compare the mechanisms of actions of a growing array of oral and injectable pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper evidence-based role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on healthcare systems.

Given the recent explosion of information on diabetes, as well as its relationship to cardiovascular diseases, we began publishing this newsletter series 16 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

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Educational Needs

This program seeks to provide physicians with the latest and most important information presented at scientific meetings this year. Unfortunately, despite the valuable information that can be gained at these conferences, the majority of practicing physicians are unable to attend them. And, given the size and scope of these meetings, attendees often miss data presentations of interest to them. Therefore, programs designed to disseminate information from these meetings on a timely basis to physicians who either cannot attend the conferences or who miss some of the presentations fulfill an educational need that would otherwise not be met.

Learning Objectives

At the conclusion of this program, the participant should be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
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- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on healthcare systems.

Target Audience

All endocrinologists and internal medicine and family practice physicians who have a special interest in and treat patients with diabetes.

Educational Methods

At the end of each conference day, a newsletter will be available on-line at www.cme.yale.edu or sent by e-mail to the office of participating physicians. Shortly after the ADA conference concludes, a Diabetes 2016 booklet (containing all of the newsletters, a program highlights summary from the program co-editors, a course evaluation form, and a sample post-test) and post-test will be available on-line at www.cme.yale.edu. The post-test must be completed on-line (not by US mail or fax).

Evaluation

A course evaluation form will provide participants with the opportunity to review the program content and method of delivery and to identify future educational needs and possible bias in the presentation.

Accreditation

This program has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Yale School of Medicine. Yale School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Designation

The Yale School of Medicine designates this enduring material for a maximum of 10 AMA PRA Category 1 Credit(s)™ (5.0 credits per test). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Medical Association has determined that physicians not licensed in the US who participate in the CME activity are eligible for AMA PRA Category 1 Credits™.
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In this issue of *Diabetes 2016* monograph, we summarize important new diabetes information that was presented at the 76th Annual Scientific Sessions of the American Diabetes Association (ADA) in New Orleans, LA.

In a packed symposium launching the 76th ADA Scientific Sessions, Dr. Kasia Lipska from Yale University reported on the grass roots operation that prompted the FDA to re-examine metformin’s use in Type 2 diabetes (T2DM) patients with mild or moderate chronic kidney disease (CKD). Two academic groups from Cornell University and Yale separately submitted Citizens Petitions to the FDA in 2013, requesting revision of the then prevailing contraindication labeling on metformin (not to be used in men with serum creatinine ≥1.5 mg/dl and, in women, ≥1.4 mg/dl). More than 3 years later, on April 9, 2016, after intensive review of the available data, the FDA changed the label stating, first, that eGFR should be used instead of serum creatinine to make prescribing decisions. Moreover, the FDA now feels that metformin can indeed be used safely in patients with mild impairment of renal function (eGFR 45-60 ml/min/1.73m²), and in some patients with moderate impairment of renal function (eGFR 30-45). They now advise assessing the benefit of continued therapy in patients whose eGFR falls below 45 and also not to begin therapy once this threshold has been reached. Metformin use remains absolutely contraindicated when the eGFR is <30—and, of course, where renal function is considered unstable. These changes to the FDA labeling will impact a significant number of patients with T2DM for whom there are more limited options for safe and effective glucose-lowering agents.

In front of an overflow crowd in New Orleans’ largest Convention Center lecture hall, the long-anticipated results of the landmark, placebo-controlled LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) were revealed. LEADER enrolled over 9,000 patients with T2DM and HbA1c ≥7% on either diet therapy or a non-incretin based glucose-lowering drug, including basal or premixed insulin. Those age ≥50 years must have had at least one definitive cardiovascular (CV) comorbidity, whereas those over 60 could have been enrolled in the absence of cardiovascular disease (CVD) if they had one additional CV risk factor. Fewer patients randomized to liraglutide experienced a primary outcome event defined as 3-point major adverse cardiovascular events (MACE) (608 [13.0%]) than did patients assigned to placebo (694 [14.9%]) (HR 0.87, p<0.001 for noninferiority; p=0.01 for superiority). CV death reduced in the liraglutide arm (219 [4.7%] vs. 278 [6.0%] for placebo; HR=0.78, p=0.007), as was all-cause mortality (381 [8.2%] vs. 447 [9.6%] for placebo; HR 0.85, p=0.02). In contrast, the effects of study drug on non-fatal MI (HR=0.88, p=0.11) and nonfatal stroke (HR=0.89, p=0.30) were not significant, although for each point estimates <1.0 suggest a modest trend toward benefit and not increased risk. LEADER demonstrated very clearly that use of this GLP-1 RA in high-risk patients has benefits on predominately atherosclerotic endpoints, on top of standard-of-care. A signal for gallbladder adverse events (145 patients on liraglutide vs. 90 on placebo) and numerical imbalance in adjudicated pancreatic malignancy in this trial (13 vs. 5 patients, respectively) needs further thought and study.

On the closing day of this year’s Scientific Sessions, investigators from the landmark EMPA-REG OUTCOME trial presented renal outcomes in T2DM patients. Previously, important CV benefits were disclosed from this multinational 7020-patient outcomes trial involving the SGLT-2 inhibitor, empagliflozin: The primary endpoint (3-point MACE) was significantly reduced in the pooled empagliflozin group (HR 0.86, p=0.0382), as was CV death (HR 0.62, p<0.0001), all-cause mortality (HR 0.68, p<0.0001), and hospitalization for heart failure (HR 0.65, p=0.0017). The speaker, Prof. Christoph Wanner, a nephrologist from the University of Würzburg, Germany, remarked that the prespecified secondary outcome of incident or worsening nephropathy was reduced by 39% in the pooled empagliflozin (10 mg, 25 mg) groups as compared with placebo (HR=0.61, p<0.001). He speculated that the effect of empagliflozin on renal endpoints likely relates to decreased glomerular barotrauma induced by afferent arteriolar vasoconstriction. This occurs because of activation of the macula densa by sodium, whose absorption is blocked proximally and thereby delivered to more distal sites along the nephron. The EMPA-REG OUTCOME trial is the first to show that a therapy alters progression of diabetic kidney disease since the ACE inhibitors and angiotensin receptor blockers (ARBs).

During the symposium entitled, “Metabolic Surgery—Is it Ready for Prime Time?,” attendees were appraised of metabolic surgery guidelines published by the 2nd Diabetes Surgery Summit (DSS-II), an international consensus conference composed of representatives of leading diabetes organizations, including the ADA. According to the DSS-II guidelines, metabolic surgery (defined as the use of gastrointestinal surgery with the intent to manage diabetes and/or obesity by addressing metabolic derangements and reducing complications to improve long-term health) should be 1) recommended for T2DM patients with BMI ≥40 kg/m², regardless of level of glycemic control, 2) recommended for T2DM patients with BMI ≥35 kg/m² with inadequately controlled hyperglycemia, and 3) considered for T2DM patients with BMI 30.0-34.9 kg/m² and inadequately controlled hyperglycemia. While these recently published and widely endorsed international guidelines for T2DM include evidence-based recommendations for the role of bariatric surgery in the care of the diabetic patient, acceptance by clinicians, patients, as well as insurance policies may be limiting factors for its mainstream use.

More details on these and other topics are found in this volume of *Diabetes 2016*. 
Metformin is expanding its reach to new populations, beyond its established use as first-line therapy for Type 2 diabetes (T2DM) and overcoming long-held contraindications. New uses are rarely realized for off-label medications due to the expense of generating trial data, but the potential benefits of metformin are being explored in several settings. Not only are there more than 100 clinical trials examining metformin use in cancer therapy, but also 2 large trials will be assessing the cardiovascular (CV) effect of metformin in people with prediabetes. The Glucose Lowering in Non-diabetic Hyperglycemia Trial (GLINT) in the United Kingdom and the Veterans Administration Cooperative Studies Program (CSP) in the US will examine the incidence of myocardial infarction, stroke, and CV mortality in thousands of individuals with pre-diabetes and at least 20% estimated 10-year risk for a CV event. These randomized, controlled trials are pursuing definitive evidence that metformin is cardioprotective, a benefit that was demonstrated in a relatively small number of metformin users in the UKPDS, but never repeated in subsequent trials.

Importantly, this past April, after an extensive safety analysis, the FDA lifted the contraindication of prescribing metformin for patients with renal impairment. Two academic groups from Cornell University and Yale simultaneously yet separately submitted Citizens Petitions to the FDA in 2013 requesting revision of the contraindication labeling on metformin. More than 3 years later, on April 9th of this year, after intensive review of the available data, the FDA changed the label stating that metformin can be used safely in patients with mild impairment of renal function, and in some patients with moderate impairment of renal function. They now advise assessing the benefit of continued therapy in patients whose eGFR falls below 45 ml/min/1.73 m². In considering whether to initiate metformin, the FDA recommends obtaining an eGFR before starting metformin, and not to initiate metformin when eGFR is between 30 and 45. Metformin use remains absolutely contraindicated when the eGFR is <30 (Table 1).

Metformin does not cause renal damage, but the prior warning in the label remained intact for decades because of the concern for lactic acidosis in patients with renal impairment and a higher risk of lactic acidosis. As Dr. Clifford Bailey of the UK presented at the same symposium, a different biguanide, phenformin, was pulled from the market in the 1970’s due to an unacceptable risk of lactic acidosis. Phenformin differs from metformin in ways that make lactic acidosis more likely. Specifically, phenformin has a longer half-life and higher concentrations in the renal tubular epithelial cells, increasing the risk of lactic acidosis.

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Table 1. Updated Metformin — CKD Prescribing Guidelines (April 2016)

- Obtain eGFR before starting metformin and annually; more frequently in those at risk for renal impairment (e.g., elderly).
- Metformin contraindicated in patients with an eGFR <30 ml/min/1.73m².
- Starting metformin in patients with an eGFR between 30-45 ml/min/1.73m² not recommended.
- If eGFR falls to <45 ml/min/1.73m², assess the benefits and risks of continuing treatment. Discontinue if eGFR falls to <30 ml/min/1.73m².
- Hold metformin at the time of / before iodinated contrast procedure if eGFR 30-60 ml/min/1.73m²; if history of liver disease, alcoholism, or heart failure; or if an intra-arterial contrast procedure is performed. Recheck eGFR 48 hours after procedure and restart if renal function stable.

half-life, appears to have greater mitochondrial activity (which correlates with a shift toward anaerobic metabolism), and 9% of people are unable to metabolize it due to a polymorphism of the hepatic enzyme, CYP206. Nevertheless, metformin was marred by this legacy, and the inherent biology of its mechanism of action. Plasma lactate levels are higher in users of metformin since metformin concentrates in the wall of the jejunum and ileum, where glucose metabolism is altered in favor of higher lactic acid generation. Dr. Bailey indicated that this activity may indeed play an important role in metformin's successful reduction of plasma glucose. However, since metformin is eliminated solely by the kidneys and unchanged by hepatic or biliary metabolism, drug levels are generally mildly increased in people with impaired renal clearance, especially below 30 ml/min/1.73 m² (Anders, Diabetes Care 2010;33:1291-1293). But as Dr. Lipska presented, this altered clearance of metformin has not resulted in significant adverse consequences for people with mild to moderate renal impairment.

No cases of lactic acidosis were reported in a meta-analysis of 347 therapeutic studies in T2DM, which included 70,490 patient-years in the metformin group and 55,451 patient-years in the comparison group (Salpeter et al., Cochrane Database of Systematic Reviews 2010; issue 4). Nearly half these studies did not exclude patients with kidney disease, making the results even more reassuring. In a separate study (Eppenga et al., Diabetes Care 2014;37(8):2218-24), the absolute risk of lactic acidosis was estimated at 7 per 100,000 person-years for current users of metformin relative to never users. Even in those with an eGFR<60, the absolute risk remained very low at approximately 16 per 100,000 person-years. Importantly, in the Reduction of Atherothrombosis for Continued Health (REACH) Registry (Roussel et al., Arch Intern Med 2010;170(21):1892-9), a subgroup analysis of metformin users with eGFR of 30 to <60, and users with eGFR <30 showed that overall mortality was no different than in patients with a eGFR ≥60, perhaps even showing a mild benefit with metformin use in the lower eGFR cohort.

In conclusion, these changes to the FDA labeling will impact a significant number of patients with T2DM for whom there are limited options for safe glucose-lowering agents. Lactic acidosis with metformin use is exceedingly rare and likely not related to drug therapy but to other medical conditions. Metformin use in patients with eGFR <60 has not been associated with worse outcomes. From the evidence, we can say the use of metformin is unlikely to substantially increase the risk of lactic acidosis in those with mild to moderate CKD (eGFR 30-60). However, large, prospective studies of metformin use in the setting of renal insufficiency are lacking. National monitoring will be important as new users with mild to moderate renal impairment are maintained or initiated on metformin. Likewise, to clinicians prescribing metformin in patients with renal impairment, we recommend reducing the dose by half once eGFR reaches 45 and monitoring eGFR every 3-4 months. The use of metformin in patients with severe CKD obviously remains inappropriate.

Cardiovascular disease (CVD) is extremely common in patients with diabetes, occurring at least 2-fold more frequently than in non-diabetic individuals. As a result, this has been a major focus of investigators presenting at international diabetes meetings. This year’s Scientific Sessions of the American Diabetes Association was no exception.

In a well attended symposium on the opening day, cardiology experts from throughout the US convened to update an audience consisting primarily of diabetes specialists on the management of heart disease in this unique patient population. Opening the symposium was Dr. Yocak Birnbaum, from Baylor University, who focused on the treatment of the patient with diabetes in the setting of acute coronary syndrome (ACS). Patients with diabetes are at increased risk of this condition, which includes unstable angina, ST-elevation myocardial infarction (STEMI) and non-ST elevation MI (NSTEMI). Moreover, post ACS, diabetic patients are more apt to develop complications, including heart failure and mortality.

Dr. Birnbaum emphasized that dysglycemia is extremely common in ACS, with studies showing that about one third of patients have known diabetes, one third either have undiagnosed diabetes or prediabetes, and only one third are normoglycemic. While hyperglycemia at presentation with ACS predicts adverse outcomes, clinical trials have shown that tight glucose control during ACS hospitalizations does not improve clinical outcomes. Accordingly, insulin infusions are no longer used routinely unless hyperglycemia is severe.

Generally speaking, the management of ACS is no different in patients with vs. without diabetes, except for greater use of coronary artery bypass over percutaneous coronary intervention (PCI) in diabetes when 2-vessel or 3-vessel disease is documented.

The next presentation was by Dr. Mikhail Kosiborod of the Mid-America Heart Institute in Kansas City, whose lecture was entitled “Management of Heart Failure in Patients with Diabetes,” clearly an area of intense interest. Dr. Kosiborod first defined heart failure as a state where the heart is unable to pump blood to meet the requirements of the body’s tissues or can do so only at the expense of high filling pressures. The diagnosis remains a clinical one, comprised of symptoms, physical exam findings, and objective tests such as chest x-ray, cardiac echo, or angiographic or nuclear ventriculography.

Heart failure is distinguished into 2 main types, based on the left ventricular (LV) ejection fraction. One form occurs due to weak pump function, i.e. with reduced ejection fraction (HFrEF). The second is that with preserved left ventricular function (HFpEF) and is the result of abnormal ventricular relaxation and filling (“stiff ventricle’’). Both result in high pulmonary vascular pressures that can culminate in pulmonary edema.

Current clinical staging and classification of heart failure are seen in Table 2 (see page 5).

Dr. Kosiborod next reviewed the increasing prevalence of heart failure, especially in the context of diabetes, describing these as ‘sister epidemics.’ Higher HbA1c levels correlate with higher heart failure risk, even levels in the minimally elevated, prediabetic range. This may relate to the effect of obesity to increase catecholamine levels, which have been associated with myocardial fibrosis. However, other factors, including inflammation, may also contribute.

The body’s response to decreased effective circulation from heart failure is ultimately counterproductive, with activation of the renin-angiotensin system, the adrenergic nervous system, and antidiuretic hormone secretion. The end result is overall deleterious neurohormonal activation and further accentuation of sodium retention.

Evidence-based therapies to improve clinical outcomes (hospitalizations, mortality) in HFpEF include ACE inhibitors and angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists, and, very recently, the combined nephrilysin inhibitor/ARB combination, sacubitril/valsartan. Digoxin and diuretics have been shown to improve symptoms only. Interestingly, no specific therapy appears to improve outcomes in HFrEF.
Next, the speaker shifted focus to the impact of diabetes therapies on heart failure outcomes. Importantly, no trial of intensive glycemic control itself has shown any benefit on the development of heart failure. Thiazolidinediones increase sodium retention in the kidney and increase both edema and heart failure hospitalization rates. They are therefore contraindicated in those with prevalent heart failure. Insulin and sulfonylureas are not ideal because they induce weight gain but have not been shown to influence heart failure rates. One DPP-4 inhibitor, saxagliptin, was found to modestly increase heart failure hospitalization, whereas such an effect was not seen with sitagliptin. There are limited data with GLP-1 receptor agonists, with a small trial (FIGHT) in HFpEF recently showing no significant benefit, but actually a trend toward worse outcomes with iragludide. Finally, the SGLT2 inhibitor, empagliflozin, reduced not only CV death but also heart failure hospitalizations in the EMPA-REG OUTCOMES trial, presumably related to the drug’s diuretic effect. There has been a lot of interest in the latter drug and drug class since the EMPA-REG results were announced. Dr. Kosiborod announced the DEFINE trial, which is measuring biomarkers and symptoms in a small group of patients with T2DM and HFpEF randomized to dapagliflozin or placebo.

During the main meeting, 3 abstracts dealing with CV complications of diabetes caught our eye. The first, from a Japanese group, dealt with HFpEF (abstract 1408-P). Toshiya et al. were interested in the relationship between albuminuria, normally considered a predictor of renal functional decline, and abnormal LV function. They longitudinally studied 730 patients with T2DM at their institution, with baseline measurements of urinary albumin excretion and echocardiograms, the latter to determine mid-wall fractional shortening (MWFS) as a measure of abnormal diastolic relaxation. Kaplan-Meier analysis and multivariable Cox regression models were used to assess the independent association between albuminuria and the incidence of HFpEF during 7.1 years of follow-up. At baseline, 602 patients had preserved ejection fraction (MWFS >26%) of whom 61 were eventually diagnosed with heart failure. Kaplan Meier curves determined that both patients with microalbuminuria (urine albumin to creatinine ratio [UACR] ≥30 but <300 mg/g creatinine [Cr]) and macroalbuminuria (UACR ≥300 mg/g Cr) experienced significantly higher rates of HFpEF than those with normoalbuminuria (ACR <30 mg/g Cr). After adjustments for age, sex, hypertension, smoking status, renal function (eGFR), and

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<th>Table 2. Staging and Classification of Heart Failure</th>
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<tr>
<td>Heart Failure Stages (ACC/AHA)</td>
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<tr>
<td>▪ No structural abnormalities or symptoms but at high risk (e.g. hypertension, coronary artery disease)</td>
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<tr>
<td>▪ Structural abnormalities of LV function but no symptoms</td>
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<tr>
<td>▪ Structural abnormalities with symptoms</td>
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<tr>
<td>▪ Refractory heart failure</td>
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<tr>
<td>Heart Failure Classification (NY Heart Association)</td>
</tr>
<tr>
<td>▪ Asymptomatic, no limitation of activity</td>
</tr>
<tr>
<td>▪ Symptoms with moderate exertion</td>
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<tr>
<td>▪ Symptoms with minimal exertion</td>
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<tr>
<td>▪ Symptoms at rest</td>
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</tbody>
</table>

HbA1c, both albuminuric groups had significantly more HFpEF. In contrast, albuminuria did not predict heart failure in patients with HFpEF.

It was concluded that these data support albuminuria as a risk factor for developing preserved ejection fraction heart failure. The investigators proceeded to suggest that both may have a common mechanism. While we agree with the first conclusion, the second seems a bit of a stretch. More likely, both albuminuria and diastolic dysfunction may simply result from long-standing diabetes, particularly when accompanied by hypertension. The investigators’ multivariable model could not assess either duration of diabetes or the quality of glycemic and hypertension control in years past. Nonetheless, based on these data, albuminuria may be considered a marker for the development of diastolic dysfunction.

One concern that persists in clinical diabetes care is whether insulin therapy could exacerbate CV risk. This is a confusing area of investigation. Hyperinsulinemia is linked to atherosclerosis, but this is related to endogenous insulin resistance, which is frequently accompanied by other features of the metabolic syndrome, namely, hyperglycemia, dyslipidemia, hypertension, and obesity—each a CVD risk factor. Endothelial dysfunction, vascular inflammation, and hypercoagulability are also demonstrated more commonly in insulin resistance. However, these data, which date back to the 1970s, cannot necessarily be used to indicate that exogenous insulin therapy aggravates underlying CV risk. Yet, some older, basic experiments had suggested that insulin might have mitogenic effects, which could be proatherogenic. Also, insulin is the therapy most commonly associated with severe hypoglycemia, which itself has been linked to increased CV mortality.

Over the years, insulin has never been shown to convincingly reduce CV events, despite its glucose-lowering and anti-inflammatory effects. The ORIGIN trial is the latest to support at least the CV safety of insulin (basal insulin glargine) in a trial of 12,537 patients with early T2DM and pre-diabetes at high CV risk. In ORIGIN, insulin doses were relatively low, however. In the ACCORD trial, our readers will recall that in the more intensively treated arm, which often required larger doses of insulin, CV mortality was increased. Thus, there remains some concern in the practicing community about the potential dangers of insulin as related to the heart—particularly in those whose therapy has resulted in significant weight gain.

With this backdrop of controversy, British collaborators, led by Anyanwug, assessed the association between insulin therapy, weight gain, and CV events in a large group of T2DM patients using a prospective observational design (abstract 1411-P). The study’s cohort consisted of 13,099 adults with insulin-treated T2DM in the UK Health Improvement Network (THIN) database. The mean age at baseline was 59 ± 14 years and mean weight, 91 ± 19 kg. One year following initiation of insulin, patients were categorized into 1 of 5 groups based on changes in weight: >5 kg weight loss, 1-5 kg weight loss, no weight loss or gain, 1-5 kg weight gain, or >5 kg weight gain. All patient outcomes were then tracked for an additional 5 years. Cox proportional hazard models and Kaplan-Meier estimates were fitted to estimate the hazards of CV events (nonfatal myocardial infarction and stroke) and all-cause death. The adjusted HRs for CV events in the respective groups, compared to the >5 kg weight loss group, were as follows: 1.00 (referent) 0.69 (95% CI: 0.54, 0.87), 0.71 (0.56, 0.89), 0.82 (0.66, 1.02) and 0.80 (0.64, 1.0), respectively. The trend was similar when the investigators focused on those individuals whose BMI was >30 kg/m² at baseline: 1.00 (referent) 0.71 (0.53, 0.94), 0.73 (0.55, 0.96), 0.78 (0.58, 1.03), and 0.68 (0.50, 0.93). In summary, there was no evidence that weight gain related to insulin therapy in a large group of patients with T2DM was associated with increased risk of CV events. Also, overall survival rates were similar between all groups.

The investigators speculated about the seemingly increased event rates in the group who lost the most weight, even suggesting that further research was needed to investigate the optimal weight target during the first year of insulin therapy.
We instead feel that their weight loss in spite of insulin therapy may be a manifestation of other health issues that could be associated with more recorded CV events. This study has several limitations including its observational design and the likelihood of unmeasured confounders. Nonetheless, it is somewhat reassuring for our insulin-treated patients who gain weight. We would also add that weight gain during insulin therapy in patients with T2DM can be mitigated by several interventions: dietary counseling, the avoidance of hypoglycemia (so that otherwise unnecessary between-meal snacking can be avoided), and the adjunctive use of non-insulin glucose-lowering therapies, such as metformin.

Finally, Gong and other Chinese investigators revealed long-term data from the landmark Da Qing study, the first to show a diabetes prevention effect from lifestyle change in patients with impaired glucose tolerance (IGT) (abstract 1388-P). In this impressive 23-year (1986 to 2009) follow-up report, the focus was on the association between CVD and the development of diabetes. The investigators noted high CV risk in Chinese IGT patients and hypothesized that this was driven primarily by those who developed actual diabetes during the study. The original Da Qing cohort comprised 577 individuals with IGT residing in a city in northeastern China. They were randomized to intensive lifestyle change consisting of diet and exercise versus standard care. The original primary outcome paper, published in 1997 (Pan et al., Diabetes Care 20:537-44), showed up to a 46% reduction in diagnosis of diabetes in the intensive lifestyle groups, later confirmed in the Finnish Diabetes Prevention Study (DPS) and the US Diabetes Prevention Program (DPP), although the risk reduction in those 2 later trials was somewhat larger at 58%, probably because of more rigorous patient training and adherence.

In the current analysis, the investigators targeted 542 (94%) of the original participants who completed 23 years of follow-up. Of these, 213 (39.3%) experienced at least 1 CV event. Sixty-three (29.6%) experienced their events before (or without ever) developing diabetes, and 150 (70.4%) experienced their events after the diagnosis of diabetes. The age-adjusted annual CVD incidence was more than 60% higher in those progressing to diabetes (18.8 [16.3-21.6]/1000 person-years vs. 11.4 [9.5-13.6]/1000 person years). Following adjustments for sex, blood pressure, cholesterol, and smoking status, developing diabetes was associated with a doubling of CV risk (HR 1.97 [1.38-2.80]).

It was concluded that the majority of heart disease risk in individuals with IGT could be attributed to that which occurs after progressive worsening of hyperglycemia to the point of T2DM. One might therefore conclude that preventing diabetes in patients with pre-diabetes might reduce their future risk of CVD. Although seemingly logical, this hypothesis remains to be proven. Since CV event rates these days are relatively low in patients with pre-diabetes, powering a study to demonstrate reduced CV risk from diabetes prevention would be very difficult.

Ways of mitigating CV risk in our patients with diabetes remains one of the key aspects in clinical care. In addition to safe glucose-lowering therapy, blood pressure and lipid management and, where indicated, anti-platelet agents such as aspirin are important.

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### The Bladder Blues

Genitourinary complications of diabetes are rarely discussed by patients and their doctors—but really should be, according to Dr. Tamara P. Bavadam, an expert in women’s urological health and project officer at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Before a packed lecture hall on the opening day of this week’s Scientific Sessions, Dr. Bavadam presented “Urologic Complications of Diabetes—Common and Often Unaddressed.”

Manifestations of diabetes involving the genitourinary tract are numerous, spanning from asymptomatic bacteriuria and urinary tract infections (UTIs), to both stress and overflow incontinence, and sexual dysfunction in both men and women. Importantly, each of these can affect quality of life; some can decrease self-esteem and lead to depression. Ultimately, there could even be a negative impact on patients’ ability to optimally manage their diabetes. For example, in one of the few well-done observational studies on this topic, Coyne et al. (Urology 2013; 82(4):799-806) found that up to one-third of patients with lower UTIs, mainly urge incontinence, had reduced their activity as a result. The primary reason given was the perceived need to urinate frequently. Some even reported non-adherence with their prescribed diuretic regimen as a result. These data underscore the complex interrelationship between urological disease and diabetes.

<table>
<thead>
<tr>
<th>Table 3. Management of Bladder Dysfunction in Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. EARLY DISEASE (urgency and stress incontinence)</strong></td>
</tr>
<tr>
<td>Stage 1: Behavior modification (scheduled voids, diuretic use timing)</td>
</tr>
<tr>
<td>Stage 2: Pharmacological therapy (antimuscarinics, beta agonists)</td>
</tr>
<tr>
<td>Stage 3: Neuromodulation therapy or botulinum toxin injections</td>
</tr>
<tr>
<td>Stage 4: Bladder denervation</td>
</tr>
<tr>
<td><strong>II. LATE DISEASE (impaired bladder emptying/overflow incontinence)</strong></td>
</tr>
<tr>
<td>Observation alone if symptoms not severe</td>
</tr>
<tr>
<td>Rule out other cause of incomplete emptying (BP H, etc.)</td>
</tr>
<tr>
<td>Cholinergic agonists</td>
</tr>
<tr>
<td>Intermittent self-catheterization</td>
</tr>
<tr>
<td>Neuromodulation therapy</td>
</tr>
<tr>
<td>Indwelling catheter</td>
</tr>
</tbody>
</table>

Increased incidence of UTIs relates to glycosuria, neurological bladder dysfunction, neutrophil dysfunction, as well as uroepithelial abnormalities that appear to encourage the growth of more virulent bacterial species. Such infections require appropriate antibiotic therapy. In contrast, asymptomatic bacteriuria is usually not treated, even in those with diabetes and abnormal renal function, for fear of stimulating the growth of resistant organisms.

Dr. Bavadam stressed that the overwhelming cause of incontinence in women with diabetes who have no clear anatomic explanation is urge incontinence related to bladder hyperactivity. While atonic or neurogenic bladder and overflow incontinence can occur, this is quite rare these days.

She concluded her remarks by emphasizing the need to ask about genitourinary health in all patients with diabetes, since patients infrequently report symptoms for a variety of reasons. In follow-up comments by the session’s chair, Dr. J. Christian Winters, a urologist at LSU Medical School, practical approaches to managing bladder dysfunction in diabetes were presented (Table 3).

Dr. Winters then reviewed the connection between diabetes and erectile dysfunction. In addition to underlying autonomic neuropathy, many
medications taken by patients with diabetes may contribute. He discussed the staged management of this common condition (Table 4).

Both speakers emphasized that optimizing blood glucose control is an important first step in managing genitourinary symptoms, with studies showing that reducing HbA1c may improve sexual dysfunction and bladder symptoms. They both agreed that patient-centered management with drug categories that control blood glucose without increasing the risk of hypoglycemia.

Table 4. Evaluation and Progressive Management of Erectile Dysfunction

- Screen for hypogonadism with morning testosterone level (x2 to confirm)
- Phosphodiesterase-5 (PDE-5) inhibitors
- Vacuum device or intracorporeal injection of vasoactive agent
- Penile prosthesis

These conditions will not only improve quality of life but also may accentuate patients’ ability to take part in healthy lifestyle habits. This, in turn, may result in long-term metabolic benefits.

**Survival in Type 2 Diabetes by HbA1c**

In a retrospective study of data from ~10% of the UK population between 2004 and 2015, Currie et al. from Europe and the US found that lower (<7%) vs. moderately elevated (≥7-<8.5%) HbA1c was associated with increased mortality risk, mainly driven by therapies known to cause hypoglycemia (abstract 173-OR). The investigators evaluated 6 glucose-lowering regimens: metformin monotherapy (n=93,915), sulfonylurea monotherapy (n=23,075), insulin monotherapy (n=10,891), combination regimens that excluded (n=129,198), or included drugs known to cause hypoglycemia (n=65,985), and regimens that included insulin plus oral drugs known to cause hypoglycemia (n=88,743).

There were 7,979 deaths over 429,022 years of follow-up. In time-dependent, multivariable models, when compared to moderately elevated HbA1c, lower HbA1c, higher HbA1c (≥8.5 to ≤9.5%), and very high HbA1c (≥9.5%) were associated with increased mortality risk with adjusted hazard ratios of 1.15 (95% CI 1.09-1.21), 1.24 (1.13-1.36), and 1.61 (1.47-1.77), respectively. Furthermore, survival varied by antihyperglycemic regimen (Figure 1). These data suggest that lower HbA1c can be achieved more safely and these conditions will not only improve quality of life but also may accentuate patients’ ability to take part in healthy lifestyle habits. This, in turn, may result in long-term metabolic benefits.

**Insights on Diabetic Neuropathy**

Diabetic peripheral neuropathy affects up to half of older T2DM patients, ranging from completely asymptomatic individuals to those having extremely painful symptoms that impact quality of life. Poster presentations this week furthered our understanding of this chronic complication of long-standing hyperglycemia.

Liu et al. from New Orleans reported that metformin exposure is associated with diabetic neuropathy (abstract 570-P). By way of background, metformin decreases serum vitamin B12 in a dose-dependent manner, which may be linked to neural dysfunction. Using a Veterans Affairs database (2004-2010), the investigators examined the effect of metformin exposure on diabetic neuropathy among 13,892 elderly (>50 years) veterans with insulin-treated diabetes who did not have neuropathy, anemia, vitamin B12 deficiency, amputation, or end-stage renal disease at baseline. Over a median follow-up period of 5.5 years, the incidence of neuropathy was 15.97 per 100-person-years. In Cox regression analyses, metformin treatment at an average dosage >750 mg/day increased neuropathy events by 37% (HR, 1.37, 95% CI, 1.28-1.48) compared with no metformin use, whereas metformin ≤750 mg/day did not (HR, 0.54, 95% CI, 0.51-0.58). HbA1c did not explain the difference in neuropathy risk between low- and high-dose of metformin (8.3% vs. 8.2%). Based on similar data presented at past meetings, it is reasonable to encourage all metformin-treated patients to take oral B12 supplements, or at the very least to periodically track serum vitamin B12 levels.

Previously thought to be a complication only of long-standing diabetes, it is now clear that even mild hyperglycemia is associated with neuropathy. The reasons for this are unclear but may be related to abnormal intracellular axonal metabolism. Peterson and Sweden coworkers found a 1% increase in HbA1c was associated with an average decrease of 0.9% (95% CI: -1.4, -0.4) in the amplitude of the suralis nerve based on neurophysiological examination in 2004 and 2014. Their study cohort included 87 individuals with normal glucose tolerance (n=36), prediabetes (n=9), or had T2DM at the initial assessment (n=42) (abstract 579-P). The investigators concluded that early diagnosis is important, with assessment in individuals with prediabetes important to prevent later development of polyneuropathy. We would point out that no one has yet demonstrated that treating prediabetes is associated with any improvement in neuropathy outcomes—certainly a study that needs to be done.

**Have You Seen My Slipper?**

TELuckingh and multinational coworkers reported a positive slipping slipper sign (SSS)—i.e., affirmative response to the question, “Have you ever lost a slipper (footwear unstrapped at the ankles) while walking without being aware that you have done so?”—identifies individuals with severe diabetic peripheral neuropathy (abstract 22-LB). In their study of 74 patients with diabetes who underwent ultrasonographic and nerve conduction studies, history of retinopathy (36.8% vs. 2.8%) and cerebrovascular accidents (18.4% vs. 13.9%) was significantly more common among those with vs. without SSS (each p<0.05). In patients with SSS, nerve conduction (latency and amplitude) was markedly diminished and maximal thickness of the right sural nerve measured by ultrasonography at the ankle and leg was reduced. SSS was also positively correlated with both Toronto Clinical and Autonomic scores and negatively correlated with nerve conduction and ultrasonographic findings.

**Editors, Yale University, New Haven, Connecticut**
Over the past decade, T2DM management has become more complex. We now have 12 individual drug classes to lower glucose. As the current ADA/EASD position statement on the Management of Hyperglycemia in Type 2 Diabetes suggests, the specific choice of pharmacologic therapy after metformin is very much dependent upon patient factors and clinician judgment (Figure 2, page 9). To date, there is no universal recommendation for which medication class to initiate next. Experience from multiple practitioners was shared in a well-attended morning symposium entitled “This Is How You Do It—Medication Options, Sequence and Combinations for Optimal Management of Type 2 Diabetes”.

Dr. Pablo Mora from University of Texas Southwestern in Dallas, kicked off the symposium by making the case for starting an injectable GLP-1 receptor agonist (GLP-1 RA) as the best second-line agent after metformin. He briefly reviewed the multiple antihyperglycemic drug classes from which to choose, sharing that, in the US, sulfonylureas are still the most commonly prescribed agent other than metformin (30.6% based on ambulatory visits in 2012; Turner LW, et al. Diabetes Care, 2014). He contended that GLP-1 RAs are a much better second-line option as they meet the “triple bottom line”: good glycemic control, low risk of hypoglycemia, and weight loss. Knowing that abnormal insulin secretion and glucagon suppression are central to the pathogenesis of Type 2 diabetes, utilization of GLP-1 RAs directly impacts these core defects of the disease.

Mora also reminded the audience that not all GLP-1 RAs are the same. As a class, they have many commonalities, yet pharmacokinetic parameters of the individual agents may dictate which of the GLP-1 RAs is more appropriate for a given patient. Generally categorized as short-acting (<24 hours) or long-acting (≥24 hours), agents with shorter half-lives have a more favorable impact on post-prandial glucose (PPG) and delayed gastric emptying, whereas, longer-acting agents tend to have greater HbA1c and fasting plasma glucose (FPG) lowering (Table 5). A recent review of head-to-head comparisons demonstrated a generally consistent impact on HbA1c lowering and differential impact on PPG and FPG as described above (Madsbad S. Diabetes Obesity Metabolism, 2016). Finally, the GLP-1 RAs are not associated with CV risk, generally demonstrate a slight decrease in blood pressure, and can be used in patients with renal impairment.

Side effects include nausea and vomiting and there remains lingering concern about pancreatic disease. The class is also the most expensive of all.

Mora closed his presentation stating: (1) metformin remains the best option for drug of first choice; (2) GLP-1 RAs help to achieve the triple goal of glycemic control, low hypoglycemia risk, and weight loss; (3) individual pharmacokinetic parameters are important when choosing a GLP-1 RA; and (4) patient preference relative to associated nausea and the delivery device should be taken into account.

Table 5. GLP-1 RAs Differentiated by Duration of Action

<table>
<thead>
<tr>
<th>GLP-1 RA Sample</th>
<th>Half-Life (hours)</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Acting (&lt; 24 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>2.4</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Lixisenatide*</td>
<td>2.7-4.3</td>
<td>EMA</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>13</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Long-Acting (&gt; 24 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>120</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>120</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Exenatide, extended-release</td>
<td>168-336</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Semaglutide*</td>
<td>155-173</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

Fernando Ovalle, MD of University of Alabama, Birmingham followed with the presentation Starting SGLT-2 Therapy Inhibitors Before Incretin Therapies—Is Empagliflozin a Game...
Changer? Dr. Ovalle reviewed the pharmacology of the SGLT-2 inhibitor class, emphasizing its significant role in glucose homeostasis. In general, each of the three drugs available in the US, canagliflozin, dapagliflozin, and empagliflozin, share similar efficacy with respect to HbA1c lowering (~0.7-0.8 decrease) with greater reductions if baseline HbA1c values are higher. Each also has a positive impact on weight and blood pressure lowering (~0.7-0.8 decrease) with greater reductions or orthostasis. Risk of bone fracture is unique to the genital mycotic infections and volume-related complications. Of these, the consequence on glucose homeostasis is most significant. In general, canagliflozin, dapagliflozin, and empagliflozin each have similar efficacy with respect to HbA1c lowering, with canagliflozin specifically having a lower risk of bone fracture. Despite some undesirable side effects, such as ketoacidosis, which is a warning for the entire class and may be related to falls, empagliflozin is emphasized as having the lowest risk of bone fracture among the SGLT-2 inhibitors.

Dr. Ovalle reiterated the size and the statistical significance of the effect of empagliflozin in this high-risk population. Outcomes trials for canagliflozin and dapagliflozin are still ongoing. The precise mechanism for improved CV outcomes associated with empagliflozin* is not understood. It is likely related to glucose and may be a result of diuresis, blood pressure control, changes in arterial elasticity, and/or sympathetic activity. He concluded the presentation describing the SGLT-2 inhibitors as a relatively new class of medications that are highly effective with positive effects on body weight and blood pressure, and generally well tolerated with improved CV outcomes in a high-risk population. Although the results need to be independently confirmed, given the magnitude of the effect and statistical significance, Ovalle is of the opinion that these medications offer significant benefits for patients with Type 2 diabetes.

Figure 2. General Recommendations for Anti-hyperglycemic Therapy in Type 2 Diabetes from the ADA and EASD

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin intolerance or contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Metformin</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>high</td>
</tr>
<tr>
<td>Weight</td>
<td>low</td>
</tr>
<tr>
<td>Side effects</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>Costs</td>
<td>Gl/lactic acidosis</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference - choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin + SU</th>
<th>Metformin + T2D</th>
<th>Metformin + DPP-4-Inhibitor</th>
<th>Metformin + SGLT2 Inhibitor</th>
<th>Metformin + GLP-1 receptor agonist</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>intermediate</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td>high</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, Fx’s</td>
<td>rare</td>
<td>GU, dehhydration</td>
<td>GI</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin + SU or T2D or DPP-4-i or SGLT2-i or GLP-1 RA</th>
<th>Metformin + SU or T2D or DPP-4-i or SGLT2-i or GLP-1 RA</th>
<th>Metformin + SU or T2D or DPP-4-i or SGLT2-i or GLP-1 RA</th>
<th>Metformin + SU or T2D or DPP-4-i or SGLT2-i or GLP-1 RA</th>
<th>Metformin + SU or T2D or DPP-4-i or SGLT2-i or GLP-1 RA</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Insulin + Mealtime Insulin or GLP-1-RA</td>
<td>Basal Insulin + Mealtime Insulin or GLP-1-RA</td>
<td>Basal Insulin + Mealtime Insulin or GLP-1-RA</td>
<td>Basal Insulin + Mealtime Insulin or GLP-1-RA</td>
<td>Basal Insulin + Mealtime Insulin or GLP-1-RA</td>
<td>----------------</td>
</tr>
</tbody>
</table>

Fx = fracture, HF = heart failure, i = inhibitor, RA = receptor agonist, SGLT = sodium-dependent glucose-linked transporter, SU = sulfonylurea, T2D = thiazolidinedione.

Diabetes Care 2015;38:140-9; Diabetologia 2015;58:429-42.
opinion that addition of an SGLT-2 inhibitor therapy after metformin is now justified.

Ilidiko Lingvay, MD, from the University of Texas Southwestern Medical Center, Dallas followed, discussing the role of immediate combination therapy with incretins plus SGLT-2 inhibitors after metformin. Sequential therapy is often inadequate. She cited the ADOPT study (NEJM, 2006) demonstrating that monotherapy in Type 2 diabetes may initially improve HbA1c, but this effect diminishes over time. Since diabetes is a multifactorial disease, intervention with a single entity is unlikely to provide a durable effect.

Invoking the DeFronzo “Ominous Octet” description (Figure 3), Lingvay contended that the pathophysiology of the disease should be addressed as extensively as possible. She also made the case that, based on the ‘legacy effect’ of good glycemic control on vascular outcomes supported by the UKPDS follow-up study, intervention should occur as early as possible.

Lingvay described the current approach to management as “treat to failure” —meaning that clinicians often wait for drugs to fail before considering additional agents. She described the alternative approach of “treat to success” to include: treating early, intensively, targeting all facets of the pathophysiology, avoiding side effects where possible, and maximizing non-glycemic benefits. From this perspective, she argued that combination therapy with an incretin mimetic, SGLT-2 inhibitor, and metformin would meet these goals. Choosing a DPP-4 inhibitor as the incretin-of-choice would allow for co-formulation and less pill burden, whereas a GLP-1 RA would enhance efficacy and weight loss. Lingvay acknowledged that data to date are limited using this approach, yet initial studies demonstrate that the combination of a DPP-4 inhibitor and SGLT-2 inhibitor as a second-line option after metformin achieves greater efficacy with a more durable effect than either agent alone with metformin (Rosenstock et al., Diabetes Care, 2015; DeFronzo R, et al., Diabetes Care, 2015). There are currently no prospective data with GLP-1 RAs in combination, but studies are on-going evaluating exenatide combining therapies with complementary mechanisms of action, such as SGLT2 inhibitors and GLP-1 RAs, but recognized that several unanswered questions remain relative to the overall efficacy, safety, and durability of this approach. We would also add that the price of simultaneously using two branded glucose-lowering drugs is formidable and would also need to be carefully considered.

While much of the enthusiasm in recent years has been directed toward these newer pharmacologic classes of medications, Alice Cheng, MD of the University of Toronto, Ontario, suggested that insulin may still be the safest alternative after metformin. She proposed that insulin’s efficacy is undisputed. When considering safety, she evaluated four parameters: (1) long-term use; (2) CV outcomes; (3) malignancy; and (4) end-organ damage. Chuckling, she shared a picture of insulin from 1922 when initially discovered by Banting and Best in Toronto and remarked that “long-term use has been tested.”

With respect to CV safety and potential for malignancy, the ORIGIN trial (NEJM, 2012) was referenced, which demonstrated a neutral effect of insulin glargine on CV outcomes and malignancies when used for over six years. Lastly, insulin is commonly and safely used in all patient types from pediatrics to pregnancy and in hepatic and renal impairment.

Cheng recognized the undesirable side effects of hypoglycemia and weight gain commonly associated with insulin use. Recent advances with long-acting agents (e.g., insulin degludec) and newer rapid-acting insulins have mitigated some of the concerns regarding hypoglycemia. Weight gain is often related to dose, thus, if insulin were initiated early, lower doses are preferred, allowing for the potential of less gain. Cheng also shared data from a recent review of studies on short term (~2-3 weeks) intensive insulin therapy initiated early in the course of disease. Outcomes such as improved beta-cell function from baseline and glycemic remission were observed. Approximately 42% of patients experienced remission even after 2 years (Kramer CK, et al. Lancet Diabetes Endo, 2013). Of course, further research is needed.

Cheng stated that insulin secretion remains a core defect in diabetes pathology, and combination therapy with other agents (incretins, SGLT-2 inhibitors) provides an alternative to maximize efficacy and minimize side effects. Insulin addresses core defects, is safe and effective, has a potential beta-cell preservation benefit, and can be mixed and matched with many options that will minimize undesirable side effects.

The symposium closed with a summary presentation from Christopher Sorli, MD, from the Billings Clinic, Montana. While displaying the different HbA1c treatment goals supported by ADA/EASD (<7.0%) and AACE (≥6.5%), Sorli made the point that population-based targets will soon be gone. Instead, practitioners should individualize targets and assure that these are well documented in the patient medical record such that the goal is consistently communicated to all caregivers. Dr. Sorli commented that a primary goal is to achieve glycemic targets safely. He also commended the ADA/EASD guideline for the patient-centric and pathophysiologic approach to the management of hyperglycemia and establishing glycemic targets. Utilizing three different patient case examples, Sorli illustrated this approach, stressing pathophysiology, uniquely defined targets for individual patients, and the need to balance benefits and adverse effects.

We fully agree with Dr. Sorli. We might add cost as an additional concern. Medication
pricing needs to be considered whenever we prescribe, especially to patients who are often taking complex polypharmaceutical regimens. In fact, although Dr. Sorli did mention the persistent role of generic drugs in the management of diabetes, we were disappointed that the symposium did not include a formal presentation on cost-effective strategies involving less expensive agents.

We feel obligated to make a few additional points when discussing the development of rationale glucose-lowering strategies in Type 2 diabetes. First, it’s critical to engage the patient in decision-making, particularly as it relates to the intensiveness of glucose control as well as the category (or categories) of medications used. The latter obviously will need to involve a frank discussion of both short-term and long-term risks. Second, if a medication is having no substantive effect on glycaemia from the outset, it should be abandoned and not blindly continued in combination with other agents. Thirdly, we must never forget that medication adherence is a key factor in drug ‘efficacy’, particularly true when prescribing more expensive agents that might require greater financial commitments from patients via higher-tiered copayments or in the context of high deductibles. Assessing adherence at each office visit is therefore key, as is the ongoing encouragement about lifestyle change, dietary modifications, and increasing physical activity.

In the end, successful diabetes management is more likely to be achieved by being as patient-centered as possible in our treatment approaches.

**Ever-Expanding Pharmacopeia?**

There are now 12 individual glucose-lowering drug classes available in the US for the management of T2DM—from those that enhance insulin sensitivity, drugs that modulate insulin supply, to categories that effect glucose absorption or excretion. Using the right medication or combination of medications will allow most of our patients to optimize their glycemic control. The question is whether we really need any new types of drugs? Several presentations this week focused on the potential future of pharmacological management in diabetes.

Agonists of peroxisome proliferator-activated receptors (PPARs) have had a complex history over the past 2 decades. The thiazolidinediones (TZDs), PPAR-γ agonists, have been available since 1997, but their popularity has plummeted over the past several years, mainly due to recognized side effects (edema, weight gain, heart failure, bone fractures) and also concerns about potential bladder cancer risk with one member, pioglitazone. With more robust data suggesting no increased risk of this malignancy and recent reports of anti-atherosclerotic effects of this inexpensive, generic drug, a resurgence in its use is possible. Dual PPAR-α,γ agonists—conceptually, a TZD plus a fibrate—were once thought to possess the perfect balance of activity to reduce insulin resistance, lower glucose, and improve lipid levels. Yet, their promise never translated to the anticipated clinical benefits, and clinical trials were halted. Active research in this area has unfortunately slowed to a snail’s pace, especially since major pharmaceutical companies have had their attention diverted to the incretin-enhancing classes of GLP-1 receptor agonists, DPP-4 inhibitors, and, most recently, the SGLT2 inhibitors.

At this week’s Scientific Sessions however, Singh and Indian colleagues reported provocative data on the combination of a new PPAR-α,γ agonist, saroglitazar*, with the SGLT2 inhibitor, dapagliflozin (abstract 73-OR). Their model was non-alcoholic fatty liver disease (NAFLD) in relatively young patients with T2DM. In South Asia, T2DM is reaching epidemic proportions. Individuals without obesity by Western criteria seem to be developing insulin resistance, fatty liver, and, all too often, CVD, at earlier ages than seen in the US. This appears to be driven primarily by dietary factors. Accordingly, there is a pressing need to understand this problem and to develop new therapies.

The investigators studied 56 patients, aged 20–35 years, who were on diet and/or metformin monotherapy for their diabetes. Hepatic fat content was assessed by transient elastography ("Fibroscan") both before and after 24 weeks of therapy with either the combination of saroglitazar and dapagliflozin (Group 1) or dapagliflozin alone (Group 2). HbA1c at baseline was 8.2±1.0% in Group 1 and 7.9%±0.6% in Group 2, decreasing to 7.1±0.4% in both groups by the end of the trial. Triglycerides were also elevated at baseline (399±83 and 374±165 mg/dL, respectively) and decreased to 183±47 and 250±30 mg/dL, respectively (between groups, p=0.002). As far as hepatic fat content is concerned, the baseline values were increased at 336±37 dB/m and 324±29 dB/m, respectively. At the end of 24 weeks, the combination therapy group’s steatosis was reduced to 205±26, a reduction of 131 dB/m (-39%) whereas the corresponding value in the dapagliflozin only group was 250±30 dB/m, down 39 dB/m (-12%) (p=0.001).

The investigators concluded that this novel combination might be a promising treatment for patients with T2DM and coexisting NAFLD, an extremely common comorbidity that increases the risk of progressive liver disease, including cirrhosis and hepatocellular carcinoma. Although improvements in transaminases were also found, no biopsies were obtained in this trial. Clearly, these data are interesting but eventually, liver biopsy data will be necessary to determine whether the reduction in fat content is accompanied by a more favorable histology that could, over time, predict reduced incidence of chronic liver disease. An entirely new category of glucose-lowering drugs are the glucokinase activators (GKAs). Glucokinase is an enzyme within pancreatic beta cells that serves, more or less, as a glucose sensor, linking intracellular glucose concentrations to insulin secretion. Activating Gk will stimulate insulin secretion, but, not surprisingly, has been associated with increased hypoglycemia rates. This and other side effects have delayed development of GKAs. However, glucokinase is also expressed in hepatocytes. Here it serves as a major regulator of endogenous glucose production. Whereas older, non-specific GKAs would have effects in both the pancreas and the liver, newer GKAs with liver specificity are now in development and have been shown to reduce ambient glucose levels but without hypoglycemia. Phase 2 data were presented this week for the investigational drug, TTP399, an oral small molecule GKA that is highly liver-specific. Sixteen drug-naïve T2DM patients (mean age 56±10 years, BMI 32±5 kg/m², HbA1c 6.9±1%) were randomized to varying doses of once-daily TTP399 (50, 200 or 400 mg) or to placebo and followed for 10 days (abstract 1140). The drug appeared to be well tolerated, and no hypoglycemia occurred on therapy. Significant reductions in fasting glucose were demonstrated in the 2 higher doses vs. placebo (-19 mg/dL, p<0.005; -21 mg/dL, p<0.05,
respectively). Also, glucose AUC (area under the curve) during a 6-hour meal tolerance test was significantly reduced with the highest dose (p<0.05). Trends toward improvement in LDL-cholesterol and triglycerides in the pooled treatment groups were also observed. The investigators concluded that their data supported moving forward with further studies of this compound.

A novel approach to managing T2DM is to focus on inhibition of glucagon, the other key glucoregulatory hormone of the endocrine pancreas. Glucagon, among other things, stimulates hepatic glucose production, predominately glycogenolysis. RN909 is a humanized monoclonal antibody that binds to and inhibits the glucagon receptor thereby impeding glucagon signaling for several months. A first-in-human study was reported this week involving 36 patients with T2DM on metformin monotherapy (abstract 110-LB). Twenty-seven patients (baseline HbA1c and FPG 8.2±0.8% and 175±36 mg/dL, respectively) received one of several single doses of RN909 (0.3, 1, 3, or 6 mg/kg) via subcutaneous injection and 9 received placebo. Dose-dependent reductions in FPG and HbA1c were found in the active therapy groups. FPG changes ranged between -21±23 and -52±12 mg/dL at 4 weeks (Figure 4). At 12 weeks, the maximal change in HbA1c was -1.5%±0.9%. Of note, however, 4 subjects on RN909 developed transient transaminitis (3X the upper limit of normal). Future studies will obviously be needed particularly from the vantage point of safety.

So, despite the already formidable pharmacopeia available to us to manage patients with T2DM, there remains intense interest in the development of newer, perhaps better tolerated drugs, most with novel mechanisms of action. Which will make it to market is anyone’s guess. Of course, the ‘bar’ may be set higher for these agents, given the emphasis by regulators on the added value of new entries to the market.

**GLP-1 Update**

Glucagon-like peptide-1 (GLP-1) receptor analogs (RAs) are among the recommended second-line agents (to metformin) for patients with T2DM (See Figure 2, page 9). Presentations made this week at the 2016 ADA Scientific Sessions add to the evidence base describing their evolving role in diabetes treatment.

**Semaglutide—An Emerging GLP-1 RA**

The results of late phase clinical development studies of the still investigational semaglutide were presented. In a double-blind, placebo-controlled, crossover study, Blundell et al. from the UK and Denmark examined mechanisms of weight loss with once-weekly subcutaneously administered semaglutide, dose-escalated to 1.0 mg, over 12 weeks, in 30 non-diabetic subjects with obesity (mean body weight=101.3 kg at baseline) (abstract 23-OR). Weight reduction was confirmed with the GLP-1 analog (-5.0±2.4 kg vs. +1.0±2.4 kg with placebo), and proportionally more fat than lean body mass was lost. Interestingly, ad lib energy intake at lunch (the primary study endpoint) and subsequent meals (evening meal, snacks) was lower with semaglutide vs. placebo (Figure 5). Fasting overall appetite score (assessed by visual analogue scale) indicated reduced appetite with the GLP-1 agonist (p=0.0023), which did not appear to be related to nausea. Other findings from the study, providing possible mechanisms for weight loss, included reduced food cravings, better control of eating, and lower relative preference for fatty, energy-dense foods.

In a 56-week, open-label, randomized study, Ahmann and coworkers from the US and Europe reported statistically significant improvements in glycemic control and weight loss with once-weekly semaglutide 1.0 mg as compared to once-weekly exenatide ER 2.0 mg, in 813 patients with T2DM (mean age 56.6 years, duration of diabetes 9.2 years, HbA1c 8.3%) who were poorly controlled on 1 or 2 oral antihyperglycemic drugs (metformin, sulfonylurea, TZD) (abstract 187-OR). Mean HbA1c was reduced by 1.5% with semaglutide and 0.9% with exenatide ER (estimated treatment difference [ETD] vs. exenatide ER -0.62%; p<0.0001). HbA1c
<7% was achieved by 67% and 40% of semaglutide- and exenatide ER-treated patients, respectively. Mean body weight (baseline 95.8 kg) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD -3.73 kg; p<0.0001). The incidence of GI adverse events was generally similar between the treatment groups (41.8% and 33.3% with semaglutide and exenatide ER, respectively), as were adverse events leading to premature discontinuation (9.4% and 7.2% for the respective treatment groups). We found this study noteworthy since exenatide ER is known as being among the most efficacious GLP-1 RAs available.

**Fixed Mixtures of GLP1-RA and Insulin**

The combined use of GLP-1 RAs and basal insulin have been shown to be as effective in lowering HbA1c as the more traditional approach of adding 3 rapid-acting insulin injections before meals to patients not controlled on basal insulin alone. A novel approach is to use fixed dose formulations of a GLP-1 RA plus a basal insulin. With these products, now FDA approved but not yet available, the dose is mainly adjusted based on that of the insulin component, with the maximal possible being that which provides the top dose of the GLP-1 RA.

For example, this week Rosenstock and co-investigators reported results of a 30-week trial in which 1170 patients with T2DM inadequately controlled on metformin ± a second oral glucose-lowering drug were randomized (2:2:1) to once-daily titratable fixed-ratio combination of insulin glargine with lixisenatide, glargine alone titrated to a fasting plasma glucose 80-100 mg/dL (maximum 60 U/day), or lixisenatide alone (20 µg maintenance dose), after a 4-week run-in period to discontinue sulfonylureas and increase metformin dose (abstract 186-OR). Greater reduction in HbA1c from baseline (8.1%) was achieved in the insulin/GLP-1 agonist arm vs. the glargine- and lixisenatide arms (-1.6%, -1.3%, -0.9%, respectively; p<0.0001), reaching mean HbA1c levels of 6.5%, 6.8%, 7.3%, respectively, at week 30. More patients reached target HbA1c <7% with the combination (74%) than glargine (59%) or lixisenatide (33%). Mean body weight increased with glargine (+1.1kg), and decreased with both the combination (-0.3 kg; difference 1.4 kg, p<0.0001) and lixisenatide alone (-2.3 kg).

Documented (≤70 mg/dL) symptomatic hypoglycemia was similar between the combination (1.44 events/year) and glargine alone (1.22 events/year), but lower with lixisenatide alone (0.34 events/year). In summary, the fixed mixed lixisenatide/glargine formulation improved glycemic control with no weight gain and without increasing hypoglycemia risk compared with glargine.

**DUAL V** study investigators conducted a post hoc analysis to determine whether patients achieving glycemic targets (HbA1c <7% or a fasting plasma glucose <130 mg/dL) also achieve composite endpoints relevant to diabetes management (abstract 239-OR). DUAL V was a 26-week open-label, treat-to-target trial that randomized 557 patients with T2DM uncontrolled on insulin glargine (20-50 U) to metformin and either once-daily IDegLira (fixed combination of the new basal insulin degludec and the GLP-1 RA liraglutide; 16 dose steps initially) or continued glargine titration. The odds of reaching a FPG target of <130 mg/dL without hypoglycemia and/or weight gain were statistically significantly higher for IDegLira- vs. glargine-treated patients (Table 6). Across baseline HbA1c groups (≥7.5), ≥7.5-<8.5, and ≥8.5), more patients achieved HbA1c <7% (87% vs. 66%; 76% vs. 50%; 59% vs. 31%), HbA1c <7% with no hypoglycemia (67% vs. 45%; 55% vs. 30%; 47% vs. 19%), and HbA1c <7% with no hypoglycemia and no weight gain (51% vs. 25%; 39% vs. 11%; 32% vs. 5%) with IDegLira vs. glargine (p<0.005 for all). Importantly, FPG and HbA1c were significantly reduced at weeks 4, 8, and 12 with IDegLira as compared to insulin glargine.

**Quadraple Therapy**

The addition of the GLP-1 RA, exenatide, and the TZD, pioglitazone, to metformin at time of T2DM diagnosis has been shown to produce greater HbA1c reduction compared to sequential addition of sulfonylurea to metformin followed by basal insulin (Diab Obes Metab 2015;17:268-75). The same research group, led by Abdul-Ghani, reported this week that adding exenatide and TZD to poorly controlled T2DM patients on maximal dose metformin/sulfonylurea leads to greater HbA1c reduction with less hypoglycemia and weight gain compared to basal-bolus insulin (abstract 188-OR). 226 T2DM patients (mean age 56 year; BMI 31 kg/m2; diabetes duration 11 years, HbA1c 10.1%) were randomized to receive once weekly exenatide plus pioglitazone (n=112) or glargine-aspart insulin (n=114) to maintain HbA1c <7%. The results are shown in Figure 6.

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**Table 6. Glycemic Control Without Confirmed Hypoglycemia or Weight Gain**: *Metformin Plus IDegLira vs. Insulin Glargine*

<table>
<thead>
<tr>
<th>Treatment Targets</th>
<th>Insulin Glargine</th>
<th>IDegLira</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG &lt;130 mg/dL</td>
<td>73.8%</td>
<td>77.7%</td>
<td>1.19</td>
<td>0.80, 1.79</td>
<td>0.3864</td>
</tr>
<tr>
<td>FPG &lt;130 mg/dL without confirmed hypoglycemia</td>
<td>40.9%</td>
<td>57.9%</td>
<td>1.95</td>
<td>1.38, 2.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FPG &lt;130 mg/dL without weight gain</td>
<td>24.0%</td>
<td>54.3%</td>
<td>4.09</td>
<td>2.80, 5.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FPG &lt;130 mg/dL without confirmed hypoglycemia and weight gain</td>
<td>14.3%</td>
<td>41.4%</td>
<td>4.55</td>
<td>2.96, 6.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c &lt;7%</td>
<td>47.0%</td>
<td>71.6%</td>
<td>3.45</td>
<td>2.36, 5.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR=odds ratio; CI=confidence interval; FPG=fasting plasma glucose; *From baseline to week 26.
†From logistic regression with treatment and region as fixed effects and baseline FPG/HbA1c (and weight gain where weight gain was included in the composite) as covariates.

Note: Confirmed hypoglycemia defined as requiring assistance or <56 mg/dL in last 12 weeks of treatment.
More patients receiving insulin failed to achieve the HbA1c goal <7% (63% vs. 17%, p<0.0001). Patients in the exenatide/TZD arm not only achieved lower HbA1c, they also had a 3.1-fold lower rate of hypoglycemia compared to patients receiving insulin (0.21 vs. 0.67 events/patient year) and gained less weight (0.7 vs. 3.1 kg). While of some interest conceptually, the notion of a 4-drug regimen for diabetes seems overly complex.

**Incretin Therapies and Risk of Pancreatitis**

Given ongoing concerns, Boyle and Bota from France (abstract 1463-P) performed a comprehensive updated meta-analysis of 18 large observational studies of GLP-1 agonists and DPP-4 inhibitors to further explore the association between incretin-based therapy and risk of pancreatitis. On the basis of results from these investigations, which included some 25,000 cases of pancreatitis, the summary relative risk (SRR) for pancreatitis with use of any incretin-based therapy was 1.13 (95% CI: 0.97, 1.31), compared to use of other antihyperglycemic medications. The risk estimate for pancreatitis among patients treated with GLP-1 agonists (from 6 independent observational studies) was 1.11 (95% CI: 0.91, 1.36), and among patients treated with DPP-4 inhibitors (from 7 observational studies) was 1.06 (95% CI: 0.77, 1.48). The investigators noted that despite point estimates greater than 1.00, the confidence intervals do not indicate any statistically significant increased pancreatitis risk when compared to other antihyperglycemic agents. They underscored, however, the important limitations of meta-analyses, including incomplete data sources, selective populations, and, particularly, inconsistent criteria for diagnosing pancreatitis. These limit drawing definitive conclusions. Carefully designed, large, prospective, population-based registry studies with appropriate follow-up and key clinical information to answer this critical safety question are still necessary. Based upon the results of their study, the investigators concluded that if their data suggest any signal for increased pancreatitis risk associated with incretin-based therapy, the degree is small.

While all of these data are very interesting, everyone is anticipating learning the results of LEADER, the largest and longest GLP-1 RA trial yet to report, and the first positive GLP-1 RA CV outcome trial. The presentation in New Orleans will be tomorrow afternoon. The question on everyone’s mind is “How strong was the treatment effect on CV events?”

**Intermittent Dieting**

Studies presented this week at the 2016 ADA Scientific Sessions reported on the benefits of intermittent dieting — with periodic reduction of calories and carbohydrates—for diabetes patients.

Carter and coworkers from Australia conducted a pilot trial to investigate the effects of intermittent compared to continuous energy restriction on glycemic control and weight reduction in 47 overweight or obese patients with T2DM (mean age 62±8.8 years, BMI 34.8±5 kg/m2, HbA1c 7.3±1.4%) (abstract 760-P). Enrolled patients were randomized to a 2-day very low calorie diet (500-600 kcals) with 5 days of habitual eating compared to a moderate, continuous energy restriction diet (1200-1500 kcals/day) for 12 weeks. Oral hypoglycemic agents, except for metformin, were discontinued and insulin was reduced at the start of the trial if HbA1c was <8% and modified during the trial in response to documented hyperglycemia or hypoglycemia. Two days of very low calorie diet vs. moderate, continuous energy restriction resulted in comparable improvements in glycemic control (HbA1c: -0.6% and -0.7%, respectively) and weight (-7.6 and -6.0 kg, respectively), reducing the need for medication (as measured by medication effect score).

In a related pilot study, Samkani et al. from Denmark reported that 2 days of dietary carbohydrate reduction, compared with a control diet (carbohydrate: 30/55% energy; protein 30/15% energy; fat: 40/30% energy, respectively), significantly improved mean glucose concentrations of 9 Type 2 diabetes patients treated with metformin monotherapy, primarily by a reduction of their postprandial glucose excursions (Figure 7) (abstract 768-P).

Taken together, these data suggest that a novel approach to diabetes care might be energy restriction only intermittently. This could potentially be an attractive option for our patients who find a consistent dietary program challenging. One could imagine that asking them to reduce calories markedly for just two days per week may be effective. Of course, the results of these preliminary investigations need to be confirmed in larger studies. And, there is always the concern of hypoglycemia when carbohydrates are restricted, particularly in those on insulin.

**Figure 7.** Mean Plasma Concentrations at Breakfast and Lunch Test Meals

*The product is not labeled for the use under discussion or the product is still investigational.*

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University, New Haven, Connecticut
In front of an overflow crowd in the largest lecture hall at the Ernest C. Morial Convention Center in New Orleans, the long-anticipated results of the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) were revealed.

As background, the GLP-1 RAs have been available as glucose-lowering agents in the management of T2DM for nearly a decade. These agents, of which four are now available in the US (exenatide, liraglutide, albiglutide, and dulaglutide) with a fifth in Europe (lixisenatide*), are still used relatively uncommonly—likely because they are injectables. The drugs are also associated with gastrointestinal (GI) side effects, particularly nausea. However, GLP-1 RA therapy is associated with weight loss (typically in the 2-4 kg range over 1 year) and some improvement in other CV risk factors. For these reasons, it has been hoped that their use might improve CV outcomes. Several agents of this class have undergone or are now undergoing assessment for cardiac safety/efficacy in large outcome trials, as mandated by the US Food and Drug Administration (FDA) since 2008. The first such trial in this class, ELIXA tested lixisenatide in ACS patients. As reported in this newsletter last June from the 75th Annual ADA Scientific Sessions in Boston (Volume 31, issue 4, page 20), the results were completely neutral—no increase or decrease in post-ACS CV events.

So, LEADER is now the second such trial to report. Its top-line results were announced a few months ago: the study was ‘positive’—i.e., patients randomized to liraglutide had a significant reduction in major adverse CV events (MACE) as compared with placebo.* The details, however, had not been revealed until today. Our readers will recall the EMPA-REG OUTCOME trial, which reported last September at the 2015 meeting of the European Association for the Study of Diabetes (EASD) in Stockholm—the first SGLT-2 inhibitor CV outcome trial to report. Therein, empagliflozin was associated with a modest 14% reduction in the hazard of MACE in over 7000 patients with T2DM and a history of CVD. More impressively, however, the MACE effect was driven predominately by a large, 38% reduction in CV mortality. Heart failure hospitalization was also reduced by 35%.* In anticipation of yesterday’s presentation, audience members wondered how similar LEADER’s results would be compared to those of EMPA-REG.

Starting the symposium, Dr. John Buse of the University of North Carolina in Chapel Hill provided a quick summary of diabetes and CVD, and specifically some background information on GLP-1 RAs. A review of the methods of this trial was next presented by Dr. Neil Poulter of the Imperial College in London. As with many of the large CV outcome studies in diabetes, LEADER was set up as a ‘non-inferiority’ trial—i.e., to first show no increase in MACE, and then once that was secured, to then demonstrate potential efficacy.

Inclusion criteria were age ≥50 years and T2DM with HbA1c ≥7% on either diet therapy or a non-incretin based glucose-lowering drug, including basal or premixed insulin. Patients had to have at least one definitive CV comorbidity. These could include coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD Stage 3 or greater, or chronic heart failure NYHA class II-III. However, in those over age 60, study participants could be enrolled in the absence of CVD if they had one additional CV risk factor, as determined by the investigator, including microalbuminuria or proteinuria, hypertension with left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or ankle-brachial index <0.9. Accordingly, LEADER participants were either undergoing, essentially, secondary prevention or primary prevention in the older group. Major exclusions included the use of mealtime insulin, prior therapy with a GLP-1 RA or a DPP-4 inhibitor, and an acute CV event within 2 weeks prior to enrollment.
Table 7. LEADER: Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Liraglutide (n=4,668)</th>
<th>Placebo (n=4,672)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome*</td>
<td>608 (13.0)</td>
<td>694 (14.9)</td>
<td>0.87</td>
<td>0.78-0.97</td>
<td>0.01</td>
</tr>
<tr>
<td>All cause death</td>
<td>381 (8.2)</td>
<td>447 (9.6)</td>
<td>0.85</td>
<td>0.74-0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>219 (4.7)</td>
<td>278 (6.0)</td>
<td>0.78</td>
<td>0.66-0.93</td>
<td>0.007</td>
</tr>
<tr>
<td>Myocardial infarction†</td>
<td>292 (6.3)</td>
<td>339 (7.3)</td>
<td>0.86</td>
<td>0.73-1.00</td>
<td>0.046</td>
</tr>
<tr>
<td>Fatal†</td>
<td>17 (0.4)</td>
<td>28 (0.6)</td>
<td>0.60</td>
<td>0.33-1.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>281 (6.0)</td>
<td>317 (6.8)</td>
<td>0.88</td>
<td>0.75-1.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke‡</td>
<td>173 (3.7)</td>
<td>199 (4.3)</td>
<td>0.86</td>
<td>0.71-1.06</td>
<td>0.16</td>
</tr>
<tr>
<td>Fatal‡</td>
<td>16 (0.3)</td>
<td>25 (0.5)</td>
<td>0.64</td>
<td>0.34-1.19</td>
<td>0.16</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>159 (3.4)</td>
<td>177 (3.8)</td>
<td>0.89</td>
<td>0.72-1.11</td>
<td>0.30</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>218 (4.7)</td>
<td>248 (5.3)</td>
<td>0.87</td>
<td>0.73-1.05</td>
<td>0.14</td>
</tr>
<tr>
<td>Microvascular events</td>
<td>355 (7.6)</td>
<td>416 (8.9)</td>
<td>0.84</td>
<td>0.73-0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>106 (2.3)</td>
<td>92 (2.0)</td>
<td>1.15</td>
<td>0.87-1.52</td>
<td>0.33</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>268 (5.7)</td>
<td>337 (7.2)</td>
<td>0.78</td>
<td>0.67-0.92</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Time-to-event analysis of first occurrence of CV death (181 in liraglutide vs. 227 in placebo), non-fatal (including silent MI (275 vs. 304) or non-fatal stroke (152 vs. 163), p-value is for superiority.
† This analysis was not pre-specified.

Data are number of patients (percentage of group) unless otherwise stated. Hazard ratios and p-values estimated using a Cox proportional-hazards model with treatment as a covariate.

In all, 9340 patients at 410 sites in 32 countries were randomized 1:1 to injections with active study drug or placebo. The study drug dose was initiated at 0.6 mg QD and progressively increased to 1.8 mg QD as tolerated. Dose reduction was allowed if side effects occurred, most commonly GI in nature (nausea, vomiting) with this drug class. Patients were then seen at periodic intervals with a planned overall maximum follow-up of 5 years. Mean time on study therapy in LEADER was 3.5 years. Study drug adherence (83-84%) and follow-up (96.8%) are excellent for a study of this size. The median dose of liraglutide during the trial was 1.78 mg/day, so few patients actually required dose adjustment.

A blinded, independent adjudication committee assessed for CV death, non-fatal myocardial infarction (MI) (including silent MI), and non-fatal stroke (3-point MACE) as the primary outcome. Secondary outcomes included the components of MACE, as well as all-cause mortality, heart failure hospitalization, and a composite microvascular outcome involving renal and eye complications.

Dr. Steven Marso of the University of Texas Southwestern Medical Center in Dallas presented the findings that fewer patients randomized to liraglutide experienced a primary outcome event (608 [13.0%]) than did patients assigned to placebo (694 [14.9%]) (HR 0.87 [95% CI: 0.78, 0.97], p<0.001 for non-inferiority; p=0.01 for superiority) (Table 7 and Figure 8). As for the individual components of the composite, CV death occurred in fewer patients on liraglutide (219 [4.7%]) than placebo (278 [6.0%]) (HR=0.78 [0.66, 0.93], p=0.007). All-cause mortality was also reduced in the liraglutide arm (381 [8.2%] vs. 447 [9.6%]) for placebo; HR 0.85 [0.74-0.97], p=0.02). In contrast, the effects of study drug on non-fatal MI (HR=0.88 [0.75-1.03], p=0.11) and nonfatal stroke (HR=0.89 [0.72, 1.11], p=0.30) were not significant, although in both circumstances the point estimates were <1.0, suggesting a trend toward benefit and not increased risk (Table 7). These data suggest that the results were driven primarily by improvements in atherosclerosis. 

(Our readers will recall that in EMPA-REG, 3-point MACE was reduced to the same degree as in LEADER [HR=0.86], but there was some heterogeneity in its components, with stroke not contributing and the point estimate being above 1.00 (HR 1.24 [0.92, 1.67]).)

With regard to LEADER’s subgroup analyses, the effect on the primary outcome appeared to be consistent across most baseline characteristics, including race, gender, CV comorbidities, and CV medications (Figure 9, on page 17). The only statistically significant interaction was that based on baseline eGFR, with better effect noted in those at <60 ml/min/1.73 m² (0.69 [0.57, 0.85]) vs. those with normal renal function (0.94 [0.83, 1.07]) (p for interaction=0.01).

There was also borderline heterogeneity for those with vs. without established CVD. The HR for the primary outcome in patients >50 years with overt CVD was 0.83 (0.74, 0.93) whereas in those >60 years with risk factors only it was 1.20 (0.86-1.67) (p for interaction=0.04).

Dr. Marso was followed by Dr. Johannes Mann of the University of Erlangen in Nurnberg, Germany, who described the other secondary outcomes, which are listed in Table 7. There was a modest trend toward reducing the frequency of hospitalization for heart failure (HR=0.87 [0.73-1.05], p=0.14). The incidence of microvascular events was also reduced in the liraglutide arm (HR=0.84 [0.73-0.97], p=0.02), driven exclusively by a reduction in new or worsening nephropathy (HR=0.78 [0.67-0.92], p=0.003). The latter was defined as new onset of macroalbuminuria, doubling of serum creatinine with eGFR <45 ml/min/m², or the need for continuous renal replacement therapy. There was actually a modest, but non-significant increase in retinopathy with liraglutide (HR 1.15 [0.87-1.52], p=0.33).

Glycemic control was improved in the active therapy group with a 0.4% (95% CI: -0.45% to -0.34%) lower HbA1c over placebo at the prespecified time point of 36 months. Liraglutide was also associated with less hypoglycemia.

Safety outcomes were then reviewed by

Figure 8. Composite Primary Outcome: Time to First Occurrence of CV Death, Non-Fatal MI, or Non-Fatal Stroke

![Figure 8](image-url)
Dr. Michael Nauck of the Bad Lauterberg Diabetes Center in Hartz, Germany. Adverse events were slightly more frequent in the liraglutide group (62.3% vs. 60.8%, \( p = 0.12 \)), but serious adverse events were balanced (49.7% vs. 50.4%, \( p = \text{NS} \)). Not unexpectedly, those treated with liraglutide had more GL side effects, such as nausea and vomiting. 77 patients on liraglutide permanently stopped study drug because of nausea and 31 for vomiting. The corresponding numbers with placebo were 18 and 2, respectively. Specific attention was paid to pancreatitis, and here the drug appeared to have absolutely no effect (18 vs. 23 patients). Acute gallstone disease, however, also occurred more commonly in the liraglutide arm (145 vs. 90 patients), including severe events (40 vs. 31 patients). Pancreatic cancer has been raised as a risk with drugs of this class by some investigators, although there was no such signal in ELIXA and large observational studies have not revealed any imbalance in the real-world setting. In LEADER, interestingly, pancreatic cancer was diagnosed in 13 patients on liraglutide and 5 on placebo (\( p = 0.59 \)), a clear imbalance, although these relatively short-term trials are certainly not powered to assess cancer risk.

Dr. Buse summarized the LEADER findings: active therapy was associated with a 13% lower risk of the primary composite MACE outcome, 22% lower risk of CV mortality, 15% lower risk of all-cause mortality, and 16% lower risk of microvascular (all renal) events. The number needed to treat to prevent one MACE over 3 years calculates to 66 (and 98 for all-cause death). Our view is that LEADER is another landmark trial in the field of diabetes. It demonstrates very clearly that use of this GLP-1 RA in high-risk patients has benefits on predominately atherosclerotic endpoints, on top of standard-of-care. The drug appears to be somewhat complimentary to the effects of empagliflozin in EMPA-REG, which appeared to predominately diminish CV death and heart failure hospitalization. Combined use of these agents is a logical conclusion, although both are exceedingly expensive and can only be considered in well-insured patients. While liraglutide was reasonably well tolerated, we think that the signal for gallbladder adverse events and also the numerical imbalance in pancreatic malignancy needs further thought and study. We would also caution not to interpret the results of LEADER to suggest that liraglutide (or for that

### Figure 9. Primary Composite Outcomes in Select Demographic and Clinical Subgroups

<table>
<thead>
<tr>
<th>Factor</th>
<th>FAS Events %</th>
<th>Liraglutide Events %</th>
<th>Placebo Events %</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>608 13.0</td>
<td>694 14.9</td>
<td></td>
<td>0.87 (0.78-0.97)</td>
<td>0.84</td>
</tr>
<tr>
<td>Female</td>
<td>3337 11.0</td>
<td>209 12.4</td>
<td></td>
<td>0.88 (0.72-1.08)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>140 11.7</td>
<td>166 14.8</td>
<td></td>
<td>0.78 (0.62-0.97)</td>
<td>0.27</td>
</tr>
<tr>
<td>≥60 years</td>
<td>468 13.5</td>
<td>528 14.9</td>
<td></td>
<td>0.90 (0.79-1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>494 13.7</td>
<td>543 15.0</td>
<td></td>
<td>0.90 (0.80-1.02)</td>
<td>0.32</td>
</tr>
<tr>
<td>Black or African American</td>
<td>47 12.7</td>
<td>59 14.5</td>
<td></td>
<td>0.87 (0.59-1.27)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>40 8.5</td>
<td>56 12.0</td>
<td></td>
<td>0.70 (0.46-1.04)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>27 12.8</td>
<td>36 20.2</td>
<td></td>
<td>0.61 (0.37-1.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index (BMI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 kg/m²</td>
<td>241 13.8</td>
<td>261 14.3</td>
<td></td>
<td>0.96 (0.81-1.15)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>367 12.6</td>
<td>431 15.2</td>
<td></td>
<td>0.82 (0.71-0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.3%</td>
<td>289 12.4</td>
<td>333 13.7</td>
<td></td>
<td>0.89 (0.76-1.05)</td>
<td>0.58</td>
</tr>
<tr>
<td>&gt;8.3%</td>
<td>319 13.7</td>
<td>361 16.1</td>
<td></td>
<td>0.84 (0.72-0.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥50 years and established CVD</td>
<td>536 14.0</td>
<td>629 16.7</td>
<td></td>
<td>0.83 (0.74-0.93)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age ≥60 years and risk factors for CVD</td>
<td>72 8.6</td>
<td>65 7.2</td>
<td></td>
<td>1.20 (0.86-1.67)</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>112 17.2</td>
<td>119 18.3</td>
<td></td>
<td>0.94 (0.72-1.21)</td>
<td>0.53</td>
</tr>
<tr>
<td>No</td>
<td>496 12.4</td>
<td>575 14.3</td>
<td></td>
<td>0.85 (0.76-0.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Antidiabetic therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 OAD</td>
<td>99 10.7</td>
<td>125 14.0</td>
<td></td>
<td>0.75 (0.58-0.98)</td>
<td>0.73</td>
</tr>
<tr>
<td>&gt;1 OAD</td>
<td>191 12.6</td>
<td>196 13.2</td>
<td></td>
<td>0.95 (0.78-1.16)</td>
<td></td>
</tr>
<tr>
<td>Insulin + OAD(s)</td>
<td>223 13.3</td>
<td>259 14.8</td>
<td></td>
<td>0.89 (0.74-1.06)</td>
<td></td>
</tr>
<tr>
<td>Insulin - OAD</td>
<td>71 19.7</td>
<td>86 22.9</td>
<td></td>
<td>0.86 (0.63-1.17)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>24 12.2</td>
<td>28 16.5</td>
<td></td>
<td>0.73 (0.42-1.25)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal function (eGFR-MDRD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>172 15.4</td>
<td>223 21.4</td>
<td></td>
<td>0.69 (0.57-0.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>eGFR ≥60</td>
<td>436 12.3</td>
<td>471 13.0</td>
<td></td>
<td>0.94 (0.83-1.07)</td>
<td></td>
</tr>
</tbody>
</table>
matter any GLP-1 RA) will have a CV benefit in patients with risk factors only but not a definite history of CVD. The drug had no obvious benefit in the former group in LEADER.

After many years of highly disappointing data with regard to glycemic control alone or through several glucose-lowering drugs, we now have two large, highly encouraging trials—first with an SGLT-2 inhibitor and now with a GLP-1 RA. The lesson we take from these landmark trials is that it may be the method in which we lower glucose that has the most significant effect on CV outcomes. We await the results of other SGLT-2 inhibitor and GLP-1 RA CV outcome trials currently underway. Lastly, it is interesting to speculate how the results of these studies will eventually be reflected in future treatment guidelines, at least for those with prevalent CVD.

It has long been established that optimal glycemic control in both critically- and noncritically-ill patients plays a significant role in improving clinical outcomes. Whereas tight glucose control in the ICU was favored prior to the NICE-SUGAR study in 2009, less stringent targets with the primary goal of avoiding hypoglycemia are now felt to be ideal. Nonetheless, management of diabetes and hyperglycemia in patients admitted to the hospital continues to be a challenge due to a multitude of factors. Hospitals across the country, and even more so around the world, vary in the approved antihyperglycemic agents carried by the formularies, the educational skills of clinicians and staff caring for patients, and technology available for providing care. Superimposed upon this variability is the often-fluctuating nutritional intake of hospitalized patients, rendering glycemic control in the hospital difficult to achieve. As a result, institutions have implemented different protocols to help them deal with these challenges. The search for effective and safe regimens for inpatient glycemic control remains the topic of numerous studies, the results of which were presented at the 2016 Scientific Sessions.

While dipeptidyl peptidase (DPP)-4 inhibitors are commonly used in outpatient management, these may be discontinued upon hospital admission mainly because they are often not approved on hospital formularies. Their ease of administration and low-risk for hypoglycemia, however, make them potentially effective for use in the hospital setting. Data presented regarding the use of sitagliptin and saxagliptin in the inpatient setting suggest that they are safe, effective, and more convenient than a traditional basal-bolus insulin regimen in noncritically ill patients.

Pasquell and co-investigators revealed results of the multicenter, prospective, open-label Sita-Hospital Trial in which 280 patients with T2DM treated with diet, oral anti-diabetic agents, or total daily insulin dose ≤0.6 unit/kg were randomized to receive sitagliptin plus glargine once daily (SITA-GLA) or a basal-bolus (BB) regimen consisting of once daily glargine plus prandial rapid-acting insulin, with both groups receiving correction doses pre-meal if blood glucose (BG) exceeded 140 mg/dL (abstract 16-OR). There were no between-group differences in mean daily BG (170±49 vs. 169±48 mg/dL, p=0.97), BG readings within the 70-180 mg/dL range (57% vs. 60%, p=0.58), or treatment failures (16% vs. 19%, p=0.54). Likewise, the number of hospital complications (acute kidney injury, wound infection, stroke, acute MI, respiratory failure, reoperation, or pneumonia, 9% vs. 7%), length of stay (median [IQR]: 4 [3-8] vs. 4 [3-8] days), and number of patients with hypoglycemia (9% vs. 12%) did not differ between the treatment groups. However, total daily insulin dose (0.23±0.14 vs. 0.33±0.16 U/kg) and number of daily insulin injections (2.2±1.0 vs. 2.0±0.9) were lower in the SITA-GLA group (both, p<0.001).

Schuman and co-investigators from Boston, MA presented findings of an open-label, controlled clinical trial in which 45 non-critically ill, hospitalized patients with T2DM whose HbA1c was ≤7.5% on one or ≤7.0% on two non-insulin antihyperglycemic agents were randomized to receive either saxagliptin plus correction insulin (n=22, aged 70±12 years, 8 men) or basal bolus insulin plus correction (control group [n=23, 68±10 years, 11 men]) (abstract 17-OR). The DPP-4 inhibitor group experienced lower mean daily BG (141.8±24.1 vs. 154.3±35.2 mg/dL, p=0.03), higher proportion of BGs in the target range of 70-140 mg/dL (51% vs. 33%, p=0.001), fewer BGs >200 mg/dL (6% vs. 18%, p=0.029), lower number of insulin injections per day (1.0±1.0 vs. 2.5±1.8, p<0.001), and lower insulin daily dose (2.0±3.3 vs. 1.4±14.4 units/day, p<0.001). The saxagliptin and control groups had similar length of hospital stay (5.2±6.3 vs. 5.3±4.4 days, respectively) and each had 1 episode of mild hypoglycemia (BG <70 mg/dL). None of the patients in the saxagliptin group required switching to basal-bolus insulin.

The choice of type of basal insulin used for inpatient management has been a subject of debate with several analog insulins now available. Galindo and colleagues did not observe any differences in glycemic control, composite of complications, or in the frequency of hypoglycemic events in a retrospective study involving non-critically ill medical and surgical patients admitted to the hospital and treated with detemir (n=624) vs. glargine (n=7476), as seen in Table 8 (abstract 19-OR).

Along with the rising prevalence of obesity and insulin resistance comes higher insulin requirements and the need for more concentrated formulations of insulin. Because of the potential for medical errors with such types of insulin, as well as the grave consequences of these mistakes, hospital formularies rarely contain concentrations other than U-100. Investigators from

### Table 8. Comparison of Detemir and Glargine in the Management of Inpatient Diabetes

<table>
<thead>
<tr>
<th>Age (years), mean ± SD</th>
<th>Detemir (n=624)</th>
<th>Glargine (n=7476)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>30.7 ± 6.8</td>
<td>30.6 ± 6.9</td>
<td>0.49</td>
</tr>
<tr>
<td>Medicine service, n (%)</td>
<td>450 (72%)</td>
<td>5106 (68%)</td>
<td>0.049</td>
</tr>
<tr>
<td>HbA1c (%), mean ± SD</td>
<td>8.3 ± 1.8</td>
<td>8.1 ± 2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Admission blood glucose (mg/dL), mean ± SD</td>
<td>186 ± 76</td>
<td>186 ± 79</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean hospital blood glucose (mg/dL), mean ± SD</td>
<td>181 ± 44</td>
<td>181 ± 45</td>
<td>0.69</td>
</tr>
<tr>
<td>Maximum first 48-hours blood glucose (mg/dL), mean ± SD</td>
<td>268 ± 85</td>
<td>271 ± 91</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Blood glucose, n (%)

<table>
<thead>
<tr>
<th>≤70 mg/dL</th>
<th>&gt;70 mg/dL</th>
<th>&lt;70 mg/dL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>210 (34%)</td>
<td>2265 (30%)</td>
<td>2265 (30%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Composite of complications, n (%)

| 205 (33%) | 2701 (36%) | 0.10 |

Mean hospital blood glucose (mg/dL), mean ± SD

| 181 ± 44 | 181 ± 45 | 0.69 |

Admission blood glucose (mg/dL), mean ± SD

| 186 ± 76 | 186 ± 79 | 0.59 |

Age (years), mean ± SD

| 63.8 ± 13 | 63.2 ± 13 | 0.25 |

BMI (kg/m²), mean ± SD

| 30.7 ± 6.8 | 30.6 ± 6.9 | 0.49 |

Medicine service, n (%) | 450 (72%) | 5106 (68%) | 0.049 |

HbA1c (%), mean ± SD | 8.3 ± 1.8 | 8.1 ± 2.1 | 0.02 |

Admission blood glucose (mg/dL), mean ± SD | 186 ± 76 | 186 ± 79 | 0.59 |

Mean hospital blood glucose (mg/dL), mean ± SD | 181 ± 44 | 181 ± 45 | 0.69 |

Maximum first 48-hours blood glucose (mg/dL), mean ± SD | 268 ± 85 | 271 ± 91 | 0.67 |

Blood glucose, n (%)

<table>
<thead>
<tr>
<th>≤70 mg/dL</th>
<th>&gt;70 mg/dL</th>
<th>&lt;70 mg/dL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>430 (69%)</td>
<td>5322 (71%)</td>
<td>5322 (71%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

| 210 (34%) | 2265 (30%) | 2265 (30%) | 0.08 |

| 33 (5%) | 406 (5%) | 406 (5%) | 0.88 |

| 205 (33%) | 2701 (36%) | 0.10 |
Pittsburgh explored the use of regular U-500 insulin in patients with markedly insulin-resistant diabetes (abstract 20-OR). The study was conducted at the VA Pittsburgh Health Care System (VAPHS) where U-500 is not stocked, but can be ordered in certain cases by endocrinologists after a discussion with the pharmacy staff. Each dose of U-500 is delivered to the ward in prefilled tuberculin syringes within 20 minutes of planned administration. U-500 was maintained (M) in 46 episodes and converted (C) to U-100 insulin in 44 episodes due to poor oral intake, renal failure, or hypoglycemia. The two groups had similar age, total daily dose, HbA1c, and markedly insulin-resistant diabetes duration, although length of stay was shorter in the group M vs. group C (3.0±0.35 vs. 4.9±0.72 days, p=0.02). Endocrine consultation was obtained in most group M patients (44/46, 96%) and fewer group C patients (26/44, 59%; p<0.001). Although total daily dose was higher in group M (194±91.5 mg/dL, group C: 81±35.3 mg/dL, p=0.02). More importantly, the incidence of hypoglycemia (BG ≤70 mg/dL) was similar between the two groups. Mean sensor glucose tended to be lower in the closed loop group (160.2±28.8 vs. 190.8±45 mg/dL, p=0.057), as was total daily insulin (48.6±26.8 vs. 69.8±44.6 units, p=0.19).

Glucocorticoid-induced hyperglycemia is often seen in patients undergoing cancer chemotherapy. In this regard, Gerards and colleagues revealed their findings on using once daily NPH insulin vs. short-acting sliding scale insulin (SSI) as add-on to their routine diabetes medication in 26 patients with T2DM treated with glucocorticoids during chemotherapy and who had a BG of >216 mg/dL during a previous chemotherapy session (abstract 74-OR). Using a continuous glucose monitor (CGM), the investigators demonstrated that glucose values were within the target range of 70-180 mg/dL 34.4% of the time using NPH and only 20.9% of the time using SSI (p<0.01) throughout 2 subsequent cycles of chemotherapy. There were no episodes of severe or symptomatic hypoglycemia.

In the hospital, glycemic control is not limited to diabetic patients. Post-surgical stress hyperglycemia in non-diabetic patients is a common occurrence. In a review of data in 2002 normoglycemic preoperative patients (BG ≤140 mg/dL) in four university-affiliated hospitals, Davis et al. from Atlanta, GA found that 21.2% developed ≥1 episode of BG 140-180 mg/dL in the time using NPH and only 20.9% of the time using SSI (p<0.01) throughout 2 subsequent episodes. Patients with stress hyperglycemia had longer lengths of hospital stay, as well as higher complication and mortality rates, compared with patients with normoglycemia. Furthermore, those with post-operative BG 140-180 mg/dL had higher risks of complications (OR 1.98 [95% CI: 1.51-2.61]) and mortality (2.82 [0.93-8.56]), while the risks for complications and mortality in those with post-operative BG >180 mg/dL were 3.36 (2.39-4.71) and 8.05 (2.92-22.17), respectively. The investigators recommended further trials to determine if treatment of stress hyperglycemia can actually improve outcomes in surgery patients. This is clearly not established based on these observational data.

Walla et al. presented results of their prospective randomized trial of inpatient glycemic control via insulin drips with different targets along with adverse outcomes up to 1 year in post liver transplant patients (n=164) with BG >180 mg/dL (abstract 1687-P). The patients were later converted to subcutaneous insulin glargine and aspart. They were also divided in two groups with half the patients having a target BG of <140 mg/dL and the other half targeting <180 mg/dL. Results are seen in Table 9 and demonstrate that tighter glucose control with a target of <140 mg/dL was associated with a decreased rate of infection but not organ rejection. The investigators concluded that glycemic control with a target of 140 mg/dL safely resulted in improved post-transplant infectious complications compared to a higher target of 180 mg/dL.

Complications arising from severe hypoglycemia in the hospital are now considered “never-events” by the Centers for Medicare & Medicaid Services. Hence, avoidance of hypoglycemia, as well as the quest to develop tools to avoid and even predict hypoglycemia, have garnered much interest in the past several years. Remote monitoring of Abbott Precision Xceed Pro™ Web Point of Care (POC) meters was used as part of an “alert” system developed to enable remote diabetes teams to quickly identify patients experiencing hypoglycemia, especially first events, with the aim of preventing their recurrence. Unique patient identifiers, ward location, date, and time were linked with capillary BG data. Rayman and UK co-investigators compared first and subsequent capillary BG ≤54 mg/dL and ≤39.6 mg/dL before (2012) and after (2013, 2014) introduction of the system (abstract 912-P). Admission numbers were similar each year.

Table 9. Results of 2 Different BG Targets in Post Liver Transplant Patients

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>140 mg/dL Group (n=82)</th>
<th>180 mg/dL Group (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>57.5±7.8</td>
<td>58.1±8.0</td>
<td>56.9±7.6</td>
<td>0.318</td>
</tr>
<tr>
<td>Pre-transplant diabetes, n (%)</td>
<td>49 (29.9%)</td>
<td>23 (28.0%)</td>
<td>26 (31.7%)</td>
<td>0.733</td>
</tr>
<tr>
<td>Mean total inpatient glucose, mean±SD</td>
<td>162.0±26.2</td>
<td>151.4±19.6</td>
<td>172.6±28.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of hypoglycemia (BG ≤70 mg/dL), n (%)</td>
<td>37 (22.6%)</td>
<td>27 (32.9%)</td>
<td>10 (12.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Any infection to 1 year, n (%)</td>
<td>89 (54.3%)</td>
<td>35 (42.7%)</td>
<td>54 (65.9%)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Adjudicated rejection, n (%)</td>
<td>37 (22.6%)</td>
<td>17 (20.7%)</td>
<td>20 (24.4%)</td>
<td>0.709</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>10 (6.1%)</td>
<td>4 (4.9%)</td>
<td>6 (7.3%)</td>
<td>0.746</td>
</tr>
</tbody>
</table>
There was a 14.9% decline over time in first hypoglycemic events ≤54 mg/dL (676, 612, 575 for 2012, 2013, 2014 respectively). Of note, the decrease was greater (37.1%) for more severe events of capillary BG <40 mg/dL (210, 139, 132 for 2012, 2013, 2014 respectively). Recurrent hypoglycemia ≤54 mg/dL decreased dramatically by 81.5% from 228 in 2012 to 42 in 2014. Similarly, recurrent severe hypoglycemic events <40 mg/dL decreased by 79.2% from 77 in 2012 to 16 in 2014. The investigators noted a minimal increase in mean capillary BG levels from 157 mg/dL to 160 mg/dL. However, this trend was not seen for episodes of significant hyperglycemia (≥360 mg/dL).

The heterogeneity of hospitals in terms of availability of subspecialty coverage, support staff, formularies, and other resources required to optimize glycemic control make the development of universal inpatient strategies nearly impossible. It would be ideal for each institution to establish its own specific methods to address this important issue. As new data emerge, and as our inpatient tools improve, hospitals will be enabled to tailor their approaches to their particular needs and patient populations.

### Kidney Kronicles

With the prevalence of diabetic kidney disease increasing in proportion to the prevalence of diabetes, the importance of early detection to delay progression is undeniable. Diabetic kidney disease is defined by albuminuria or a decrease in GFR in patients with diabetes. Dr. Amy Mottl from Chapel Hill, NC began a symposium entitled, “Paradigm Shifts in Diabetic Kidney Disease,” by briefly discussing the role of microalbuminuria in diabetic nephropathy. While microalbuminuria highly correlates with clinical outcomes and is a major predictor of death and progression to kidney disease and CVD, reliance on it to diagnose diabetic kidney disease is fraught with challenges.

For example, normal albumin excretion can be seen despite a decline in eGFR, with microalbuminuria occurring after a significant fall in eGFR. While the presence of macroalbuminuria is an unequivocal sign of kidney disease, the degree of microalbuminuria also does not correlate with the degree of nephropathy. This is largely due to the fact that microalbuminuria as a measure can be somewhat labile and may in fact be reversible.

In a study by Krolewski et al. (Diabetes Care, 2014) comprising Type 1 diabetes (T1DM) patients with normoalbuminuria versus microalbuminuria, renal function decline was found to begin during the normoalbuminuric phase. The strongest determinants of renal function decline were actually baseline serum uric acid levels and an experimental marker, tumor necrosis factor receptor 1 and 2, but not urine albuminuria.

Dr. Mottl also cautioned about using the

### Table 11. Histologic Changes Associated with Disease Mechanisms of Diabetes

<table>
<thead>
<tr>
<th>Disease Mechanism</th>
<th>Albuminuria (Micro/Macro)</th>
<th>Decreased eGFR (&lt;60 mg/min/1.73m²)</th>
<th>Predominant Histologic Change</th>
<th>Risk for Rapid Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>++++/+++</td>
<td>+++</td>
<td>Mesangial expansion</td>
<td>+++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++/+</td>
<td>++</td>
<td>Arteriosclerosis</td>
<td>+++</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>+/-</td>
<td>++</td>
<td>Arteriosclerosis</td>
<td>++</td>
</tr>
<tr>
<td>Obesity</td>
<td>++++/++</td>
<td>++</td>
<td>Focal segmental glomerulosclerosis</td>
<td>+</td>
</tr>
<tr>
<td>Aging</td>
<td>+/-</td>
<td>+</td>
<td>Arteriosclerosis, interstitial fibrosis</td>
<td>+</td>
</tr>
</tbody>
</table>

KDIGO (Kidney Disease: Improving Global Outcomes) definition of rapid decline in kidney function as loss of ≥5 ml/min/1.73 m² per year of eGFR. She gave the example of such a loss from 90 ml/min/1.73 m² to 85 ml/min/1.73 m² over a year in one patient followed by stabilization of eGFR vs. a loss of 15 ml/min/1.73 m² from 90 ml/min/1.73 m² to 75 ml/min/1.73 m² over the course of 3 years, which represents a total drop of 16%. Though both may meet criteria for “rapid decline in kidney function,” the latter scenario is more concerning, reflective of a more progressive form of nephropathy. She proposed that in some cases, considering percent loss over time may be more accurate in depicting the true clinical picture.

Assessing GFR itself in patients with diabetes is also challenging. Measured GFR normally fluctuates by 5 to 10%, more so in patients with diabetes. Moreover, hyperfiltration has been demonstrated to occur transiently during periods of hyperglycemia. Cystatin-C is now thought to be superior to creatinine measurements in estimating GFR. Cherney and colleagues from Toronto (Diabetic Medicine, 2010) examined measured GFR using inulin clearance (GFR_inulin), and two estimates based on plasma measurements—eGFR_MDRD and eGFR_Cystatin-C—in 32 normotensive, normoalbuminuric patients during clamped euglycemia and hyperglycemia. Increase in GFR_Cystatin-C appeared to be similar to that in measured GFR, while GFR_MDRD demonstrated a decline, as seen in Table 10.

It is important to note that the presence of microalbuminuria, as well as eGFR, is simply a surrogate of diabetic kidney disease. The ultimate determinant of the presence of the condition is a renal biopsy in which diabetic glomerulosclerosis with mesangial expansion, with or without Kimmelstiel Wilson nodules, are seen. Such changes may also be seen in other conditions like arteriophlebsclerosis, obesity glomerulopathy, and interstitial fibrosis due to aging.

Mottl then proceeded to discuss the disease mechanisms in diabetes and the resulting predominant histologic change. It is interesting to note variation in the degree of albuminuria and the decline in eGFR associated with these mechanisms (Table 11).

The complex nature of diabetes, the various ages of patients, and degrees of superimposed hypertension, atherosclerosis, obesity, as well as the degree of hyperglycemia in diabetic patients result in the wide histopathology spectrum of diabetic kidney disease. Given the pitfalls of using microalbuminuria and the challenges in estimating GFR to be used in the diagnosis of CKD, Dr. Mottl
proposed the more frequent use of kidney biopsies to confirm diabetic kidney disease. Biopsies are undoubtedly superior at depicting severity and progression of disease. Because of this, in her professional experience, biopsy results have often motivated her patients to strive to improve glycemic control. However, she admits that this may not be as readily available or accepted by patients as are less invasive measurements, namely microalbumin and eGFR.

“How Much of End-Stage Renal Disease is Attributable to Diabetes” was the title of the next speaker’s talk. Dr. Kevin Abbott of Washington, MD discussed results of several studies showing that 53% to 63% of ESRD in diabetes patients is due to non-diabetes-related renal disease. He also noted ethnicity as a major risk factor in the development of kidney disease, with blacks being at highest risk.

Dr. Harold Feldman from Philadelphia, PA presented results from the Chronic Renal Insufficiency Cohort Study (CRICs). This is a US multicenter, prospective study of racially and ethnically diverse patients with CKD. It originally aimed to identify novel predictors of CKD progression and to elucidate the risk and manifestations of CVD among nearly 4,000 individuals.

Study investigators found that blacks with high-risk apolipoprotein L1 (APOL1) gene, regardless of diabetes status, progressed faster to renal outcomes than those with low-risk variants (Denker, Clin J of Am Soc Neph 2015). After adjusting for traditional risk factors and socioeconomic characteristics, regardless of diabetes status or APOL1 genotype, this racial group still had a higher risk of ESRD.

The speakers agreed with some members of the audience who commented that although we are improving ways to diagnose diabetic kidney disease and discovery of novel markers and risk factors is occurring, treatment remains the same for now, and definitely a fertile topic for future research.

Closing the Loop

The results of promising work on several fronts for high-tech management of Type 1 diabetes mellitus (T1DM) were presented this week.

In a brief, random-order cross-over study, Elkhatib and US investigators compared glycemic regulation with a bihormonal “bionic pancreas” to that with a conventional insulin pump over 11 days each in adults with T1DM living at home and performing their normal activities without restrictions on diet or exercise (abstract 77-OR). During the bionic pancreas arm, data from a CGM were used by an autonomously adaptive algorithm to control subcutaneous delivery of both insulin and glucagon. During the comparator arm, participants managed their own insulin pump. In the cohort of patients who completed both arms of the study, the bionic pancreas was associated with a reduction in the mean number of daily symptomatic hypoglycemia events (0.6±0.6 vs. 0.9±0.6 events/day, p=0.023). The mean total daily dose of insulin delivered by the bionic pancreas varied widely between participants and was ~6% greater during the bionic pancreas period than during the comparator period (0.66±0.15 vs. 0.62±0.18 U/kg/day, p=0.01).

In another random-order cross-over study, Eklhaspour and coworkers from Boston compared 2 insulin-only configurations of a bionic pancreas (glucose targets of 130 and 145 mg/dL also with a bihormonal configuration (glucose target of 130 mg/dL), and usual care (patient-managed insulin pump therapy) in T1DM patients (abstract 79-OR). Study participants went about their daily routines with no limitations on diet or exercise during each 3-day test period. Based on CGM, there was no significant difference in aggregate mean glucose and time <60 mg/dL between the bihormonal 130 mg/dL target configuration (156±12 mg/dL, 0.6±1.0%), the insulin-only 130 mg/dL target configuration (161±17 mg/dL, 0.8±1.4%), and usual care (158±31 mg/dL, 1.4±2.6%). Mean CGM glucose for the insulin-only 145 mg/dL target configuration was higher (174±23 mg/dL) than both 130 mg/dL target configurations and usual care (p=0.0014, <0.0001, and 0.034, respectively) with no significant reduction in time <60 mg/dL (1.0±1.5%). There were no significant differences in insulin total dose among any of the bionic pancreas arms. Based on these findings, the investigators suggested further study of insulin-only biionic pancreas configurations with glucose targets set lower than 130 mg/dL.

We continue to be impressed by the advances made in the field of CGM and in the development of an ‘artificial pancreas’—i.e., an insulin pump (with or without a glucagon pump) driven by the sensor’s data. It is our hope that, within a few short years, the regulatory hurdles will be surpassed and viable commercial units will finally be available for our T1DM patients.

So Many Posters, So Little Time....

Infection in Elders with Poor Glycemic Control

Using data from the Royal College of General Practitioners Research and Surveillance Centre, a primary care sentinel network, McGovern and associates from the UK performed a retrospective cohort analysis of older people with diabetes to determine the impact of glycemic control on incident infectious diseases in 2014 (abstract 1460-P). In the population (n=649,844), they identified 19,806 people with diabetes (19,534 Type 2, 272 Type 1) aged ≥65 years. Of these, 6,741 (34.0%) had moderate glycemic control (HbA1c 7.0-8.5%) and 2,199 (11.1%) had poor glycemic control (HbA1c >8.5%). After adjusting for patient demographics, smoking status, diabetes type, comorbidities, and medication use, poor glucose control was a predictor of incident pneumonia (OR 2.38; 95% CI: 1.44-3.93; p<0.001), urinary tract infection (OR 1.28; 95% CI: 1.06-1.55; p=0.012), skin infections (OR 1.30; 95% CI: 1.10-1.54; p=0.002), and genital candida (OR 3.74; 95% CI: 2.44-5.75; p<0.001). Moderate control was only associated with increased risk of genital candida (OR 1.58; 95% CI: 1.06-2.35; p=0.026). In contrast, the incidence of influenza-like illness was not related to glycemic control.

* The product is not labeled for the use under discussion or the product is still investigational.

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University,
New Haven, Connecticut
Investigators from the EMPA-REG OUTCOME trial presented an update on the closing day of this year's ADA Scientific Sessions. The main new data consisted of the renal outcomes in T2DM patients from this landmark study. Previously, important CV benefits were disclosed from this multinational 7020-patient outcomes trial involving the SGLT-2 inhibitor, empagliflozin. Prof. Chrisoph Wanner, a nephrologist from the University of Wurzburg, Germany, presented the prespecified secondary outcome of incident or worsening nephropathy. This was defined as the composite of:

- progression to macroalbuminuria (UACR >300 mg/g) or
- doubling of serum creatinine accompanied by eGFR (MDRD) ≤45 mL/min/1.73m² or
- initiation of renal replacement therapy or
- death due to renal disease

The outcome was reduced by 39% in the pooled empagliflozin* (10, 25 mg) groups as compared with placebo (HR=0.61 [95% CI: 0.53, 0.70], p<0.001) (Figure 10). Importantly, this is the first time that any therapy has been shown to alter the progression of diabetic kidney disease since the ACE inhibitors and ARBs. Next, Dr. Wanner presented subgroup analyses, and there was no heterogeneity in the treatment effect based on age, sex, race, BMI, baseline HbA1c, measures of renal function, urinary albumin status, or any background therapy of renin-angiotensin system (RAS) blockers. As with the CV outcomes, there was also no significant difference in the treatment effect with either dose of the SGLT-2 inhibitor. Dr. Wanner also emphasized that the renal composite was not driven solely or even predominately by the ‘softer’ endpoint of progression to macroalbuminuria. In fact, there were substantial reductions in all of the components, with all but renal death (small numbers) achieving statistical significance on their own (Figure 11).

**Figure 10. Incident or Worsening Nephropathy**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4124</td>
<td>3994</td>
</tr>
<tr>
<td></td>
<td>3624</td>
<td>3668</td>
</tr>
<tr>
<td></td>
<td>3711</td>
<td>2579</td>
</tr>
<tr>
<td></td>
<td>2503</td>
<td>1607</td>
</tr>
<tr>
<td></td>
<td>1219</td>
<td>280</td>
</tr>
</tbody>
</table>

Kaplan-Meier estimate. Hazard ratio based on Cox regression analyses.

**Figure 11. Incident or Worsening Nephropathy and its Components**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124</td>
<td>388/2061</td>
<td>0.61 (0.53, 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset macroalbuminuria</td>
<td>459/4091</td>
<td>330/2033</td>
<td>0.62 (0.54, 0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Doubling of serum-creatinine*</td>
<td>70/4645</td>
<td>60/2323</td>
<td>0.56 (0.39, 0.79)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>13/4687</td>
<td>14/2333</td>
<td>0.45 (0.21, 0.97)</td>
<td>0.0409</td>
</tr>
</tbody>
</table>

*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m².
Cox regression analyses.
The empagliflozin groups experienced an initial small rapid decrease in eGFR (likely due to volume changes from this medication, which has osmotic diuretic properties). Subsequently, there was stabilization, whereas the placebo group’s eGFR fell slowly over time. Interestingly, however, there was no decrease in incident albuminuria in patients with normoalbuminuria at baseline.

Prof. Wanner speculated that the effect on renal endpoints with empagliflozin likely relates to decreased glomerular barotrauma induced by afferent arteriolar vasoconstriction. This occurs because of activation of the macula densa by sodium, whose absorption is blocked proximally and thereby delivered to more distal sites along the nephron.

It is difficult to compare one study with another due to varying designs, durations of treatment, and patient populations. However, the effect of liraglutide on renal outcomes, as presented yesterday in LEADER, was comparatively more modest, and driven by the macroalbuminuria component.

So, empagliflozin is now reported to have both CV and renal benefits. It will be of great interest if these data can be confirmed with other members of this medication class.

**Diabetes: A Surgical Disease?**

The exponential increase in prevalence of diabetes is related to the rise in obesity. Over the past several years, there has been increasing effort targeted at discovering and developing methods to manage obesity, among these being bariatric or what some refer to as ‘metabolic’ surgery. However, despite the growing evidence that metabolic surgery improves T2DM, independent of weight loss, current treatment algorithms do not include this option. Furthermore, clinicians and patients remain inadequately informed about the indications, benefits, and risks of surgical treatments. Moreover, insurance reimbursement policies typically focus on weight/BMI-centric criteria and do not include diabetes-related metrics—so those with diabetes may not be adequately prioritized when it comes to access to the procedure.

The symposium entitled, “Metabolic Surgery—Is it Ready for Prime Time?” held at the Great Hall B during the third day of the ADA Scientific Sessions, focused on the recently published metabolic surgery guidelines of the 2nd Diabetes Surgery Summit (DSS-II), an international consensus conference composed of representatives of leading diabetes organizations. The ADA played a role in developing and ratifying these guidelines. Furthermore, they were widely endorsed by international organizations including the American Association of Clinical Endocrinologists (AACE), the Endocrine Society, American College of Surgeons, American Society for Metabolic and Bariatric Surgery, and the European Association for the Study of Obesity. The treatment algorithm as recommended by the participants is seen in Figure 12.

Metabolic surgery is defined as the use of gastrointestinal surgery with the intent to manage diabetes and/or obesity by addressing metabolic derangements and reducing complications to improve long-term health. There are several types of surgeries (Figure 13, on page 24), each with their own effect on weight and metabolism. Among them, the Roux-en-Y gastric bypass (RYGB) appears to be the most commonly performed procedure that has the most favorable effects on glycemia and weight in T2DM. This entails dividing the stomach into two compartments, leaving only the small upper chamber in digestive continuity with the food passing from this area to the proximal jejunum, thereby bypassing most of the stomach, duodenum, and small portion of the jejunum.

A vertical sleeve gastrectomy (VSG) on the other hand involves excision of the body and fundus of the stomach, leaving a narrow sleeve along the lesser curvature, with nutrients following the normal route through the GI tract. It has led to excellent weight loss and major improvement of T2DM in short- to medium-term studies and may be a feasible option in patients for whom bowel diversion may involve a greater risk.

A laparoscopic adjustable gastric band (LAGB) is an inflatable silicone ring encircling the upper stomach and may be adjusted to optimize the diameter of a tight aperture that hinders food flow. The effect of this in glycemic control is related to the degree of weight loss. It is, however, associated with a greater risk for reoperation/revision due to failure or band-related complications.

Finally, biliopancreatic diversion (BPD) is the least common procedure and results in bypassing a large majority of the small intestine causing malabsorption. While clinical evidence suggests that this may be the most effective in glycemic control and weight loss, it is associated with a significant risk of nutritional deficiencies, making it less favorable. Consideration for its use should be reserved for patients with extreme obesity (BMI ≥60 kg/m²).

**Figure 12. Metabolic Surgery Guidelines for T2DM**

<table>
<thead>
<tr>
<th>Patients with Type 2 Diabetes</th>
<th>Nonobese BMI &lt;30 kg/m² or &lt;27.5 for Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III Obese BMI ≥40 kg/m² or ≥37.5 for Asians</td>
<td>Expeditied assessment for metabolic surgery</td>
</tr>
<tr>
<td>Optimal lifestyle and medical RX</td>
<td>Optimal lifestyle and medical RX (including injectable meds and insulin)</td>
</tr>
<tr>
<td>Class II Obese BMI 35.0-39.9 kg/m² or 32.5-37.4 for Asians</td>
<td>Class I Obese BMI 30.0-34.9 kg/m² or 27.5-32.4 for Asians</td>
</tr>
<tr>
<td>Class II Obese with poor glycemic control</td>
<td>Class II Obese with adequate glycemic control</td>
</tr>
<tr>
<td>Class I Obese with poor glycemic control</td>
<td>Class I Obese with adequate glycemic control</td>
</tr>
<tr>
<td>Recommend metabolic surgery</td>
<td>Consider metabolic surgery</td>
</tr>
<tr>
<td></td>
<td>Nonsurgical treatment</td>
</tr>
</tbody>
</table>
Dr. Philip Schauer from the Cleveland Clinic began the symposium by comparing recommendations regarding metabolic surgery from the ADA Standards of Medical Care and DSS-II. Bariatric surgery, according to the ADA Standards of Medical Care 2016, may be considered for adults with BMI >35 kg/m² and T2DM. At the time of publication, however, there was insufficient evidence to generally recommend surgery in patients with BMI ≤35 kg/m². The recommendations go on to state that patients with T2DM who have undergone bariatric surgery need lifelong lifestyle support and annual medical monitoring.

In contrast, DSS-II guidelines state that for patients with T2DM, metabolic surgery should be:
- **Recommended** in patients with BMI >40kg/m², regardless of level of glycemic control
- **Recommended** in patients with BMI ≥35kg/m² with inadequately controlled hyperglycemia
- **Considered** in patients with BMI 30.0-34.9 kg/m² and inadequately controlled hyperglycemia.

Schauer cautions against the universal use of BMI cut-offs for all patients. Specifically, visceral fat, and therefore insulin resistance, is higher in the Asian population compared to Caucasians with the same BMI. Hence, DSS-II guidelines recommend BMI cut-offs above be decreased by 2.5 kg/m² in Asians.

Metabolic surgery, RYGB and BPD in particular, was shown in several studies to induce initial remission of T2DM in the most severely obese adults, although many of these relapse to overt T2DM at some point. It is logical to presume, but remains unproven, that remission of T2DM resulting from metabolic surgery impacts micro- or macrovascular complications. This is primarily because long-term (≥5 years) metabolic studies whose outcomes are micro- and macrovascular complications are largely observational and do not include randomized clinical trials (RCT). Dr. David Nathan of the Massachusetts General Hospital in Boston identified this as evidence “gap”, elaborating the need for longer-term, large-scale, adequately controlled studies that investigate the effects on relevant clinical outcomes. For now, the early findings of a 3-year RCT suggest microvascular benefits of bariatric procedures (STAMPEDE trial, Schauer et al. Diabetes Care 2014). Nathan also stated a growing demand for additional clinical trials evaluating procedures that are more commonly used in practice. He adds that there is a need for studies examining the balance between improved metabolic control over time and benefits with regard to micro- and macrovascular complications, quality of life, post-operative morbidity and mortality, and costs of surgery.

To date, the evidence basis is small. There have been 11 trials comprising less than 800 randomized patients in total, followed over 1 to 5 years. All but one study found surgery to be superior to medical therapy in terms of weight loss, HbA1c reduction, T2DM remission, triglyceride level, HDL level, remission of metabolic syndrome, quality of life, and medication reduction. Surprisingly, most studies did not reveal a difference in blood pressure control or LDL, although there was a bigger need for reduction in medication doses. In the studies, there were no perioperative CV-related events or deaths. The most common complications were anemia (15%), reoperation (8%), and GI (5%). Of note, hypoglycemic events were not found to be different from the control (medicine-treated) group.

All the speakers agreed that the story does not quite end after surgery. The patients should continue to be managed indefinitely after surgery by multidisciplinary teams including endocrinologists, surgeons, nutritionist, and nurses with specific diabetes expertise. Follow-ups should occur every 6 months for the first 2 years post-operatively, and at least annually thereafter. Rigorous long-term, lifestyle changes are at utmost importance in maintaining benefits achieved by surgical weight loss. The guidelines recommend monitoring glycemic control with the same frequency as in standard diabetes care. In patients whose glycemia has been normalized, glucose control should be evaluated similarly to that of patients with prediabetes due to the potential for relapse. In those with a stable condition of non-diabetes glycemia for less than 5 years, monitoring for diabetic complications at the same frequency prior to remission is recommended. Of course, it is also important to monitor adherence with vitamin and mineral supplements required after certain procedures.

In summary, the evidence for metabolic surgery as a safe and effective treatment for T2DM is growing. The most recent, widely-endorsed international guidelines for T2DM now include evidence-based recommendations for its role in the care of the diabetic patient. Overall acceptance by clinicians, patients, as well as insurance policies may be limiting factors for its mainstream use.
The Insulin Resistance Intervention after Stroke (IRIS) trial was recently published (Kernan WN et al., *N Engl J Med* 2016). This study tested the hypothesis that improving insulin sensitivity with the TZD, pioglitazone, in 3876 insulin-resistant but non-diabetic stroke patients would reduce future vascular events. This was indeed confirmed, as the group randomized to the TZD experienced a highly significant 24% reduction in fatal/non-fatal stroke and myocardial infarction (p=0.007) over 4.8 years. * At the Presidential Oral Abstract session on the concluding day of this week’s meeting, Dr. Silvio Inzucchi from Yale School of Medicine presented the diabetes outcome data from IRIS.

TZDs have previously been shown to prevent or delay the development of T2DM in patients with IGT, a variant of prediabetes, with risk reductions in the 63-72% range. In IRIS, diabetes was diagnosed on the basis of annual FPG levels or if the diagnosis was made by the patient's own physician outside of the trial. Patients assigned to pioglitazone experienced a 52% reduction in the hazard of diabetes (3.8% vs. 7.7%; HR 0.48 [95%: CI 0.33, 0.69]; p<0.001). * This effect was predominately driven by those who were most metabolically deranged at baseline. That is, the vast majority of the absolute risk reduction was observed in participants with prediabetes as categorized by FPG 100-125 mg/dL (HR=0.41 [0.30, 0.57]) or by HbA1c >5.7% (HR=0.46 [0.34, 0.62]), as well as by patients with the highest HOMA-IR values (HR=0.46 [0.34, 0.62]) and those with metabolic syndrome (HR=0.46 [0.33, 0.63]).

As with other TZD trials, weight gain occurred more commonly in the active therapy group and the frequency of bone fractures was increased (5.1% vs. 3.2%). However, no increase in heart failure or in cancer rates was seen.

Dr. Inzucchi pointed out that pioglitazone can now be considered the only oral diabetes drug to reduce atherosclerotic CV events. * Moreover, it is the only drug demonstrated to prevent diabetes and improve CV outcomes in the same trial, although these two effects are not necessarily linked. Whether these data are enough to revitalize interest in this TZD remains to be seen.

**More on SGLT-2s**

Sodium-glucose cotransporter (SGLT-2) inhibitors promote glucosuria and renal calorie losses via the blockade of a key glucose transporter located on the luminal surface of proximal tubular cells that normally serves to reclaim 90% of the filtered glucose load. Use of this class is associated with modest HbA1c reductions in the range of 0.6-0.9%, improvements in blood pressure (-4/2 mmHg), and a small decrease in weight loss on the order of 2 kg. Side effects include frequent urination, the potential for dehydration, increased risk of genitourinary infections (mainly mycotic in origin), and diabetic ketoacidosis (DKA). The latter was initially described in Type 1 diabetes patients taking the drug in an off-label fashion although reports have emerged of this diabetic emergency in T2DM as well.

Within the past year, important findings from the EMPA-REG OUTCOME trial were announced (see *Diabetes 2015*, Volume 32, Edition 3, see page 16). This 7000+ patient trial demonstrated, for the first time with any diabetes medication, a 14% relative reduction in major adverse CV events (MACE) in those participants randomized to one of two doses of the SGLT-2 inhibitor empagliflozin* versus placebo. This effect was primarily driven by a surprising 38% reduction in CV death—also never before seen in the context of any diabetes therapy. A 35% reduction in hospitalization for heart failure was also demonstrated.

Because of these results, there is increasing interest from both the diabetes and cardiology communities in the entire drug class, although it remains uncertain whether ongoing large CV outcomes trials with the two other SGLT-2 inhibitors available in the US (canagliflozin [CANVAS, CANVAS-R, CREDENCE] and dapagliflozin [DECLARE]) will show similar results.

**Renal Effects**

Several other presentations focused on this oral glucose-lowering category's non-glycemic effects. Lamberts Heerspink and international collaborators presented *post-hoc* renal data from a canagliflozin clinical trial, seeking to determine whether the drug had any effect on urine albumin excretion or eGFR independent of its effects on hyperglycemia (abstract 70-OR). 1450 T2DM patients had been randomized in an earlier glycemic trial to canagliflozin 100 or 300 mg OD or glimepiride (6-8 mg OD). As previously reported, the HbA1c changes in these groups were -0.82%, -0.93%, and -0.81% at 1 year and 0.65%, 0.74% and 0.55% at 2 years, respectively.

New clinical endpoints for the current study included UACR and eGFR over 2 years. The annualized decline in eGFR proved to be 3.3 ml/min/1.73 m² (95% CI: 2.8-3.8) in the sulfonylurea-treated group and 0.5 (0.0-1.0) and 0.9 (0.4-1.4) ml/min/1.73 m² in the 100 mg and 300 mg canagliflozin groups, respectively. In those with UACR >30 mg/g Cr, urinary albumin excretion was also reduced with SGLT-2 inhibition as compared to glimepiride: -31.7% (8.6-48.9%, p=0.01) and -49.3% (31.9-62.2%, p<0.001) with 100 and 300 mg of canagliflozin, respectively.

The investigators concluded that canagliflozin appeared to slow the progression of kidney disease* compared to sulfonylurea therapy, changes which were not likely related to improvements in glycemic control.

**How Do They Stack Up vs. DPP-4 Inhibitors?**

Investigators have explored how these agents might compare with another popular newer drug class, the DPP-4 inhibitors, which exert their effect through the incretin system. This is an important clinical question because both classes are endorsed as reasonable options by professional organizations, including the ADA, once monotherapy with metformin no longer adequately controls glucose. The DPP-4 inhibitors are somewhat unique amongst glucose-lowering drugs as not being associated with any common adverse effects, although there remains the possibility that they may modestly increase the risk of pancreatitis. Mishriky and American colleagues conducted a meta-analysis of previously published trials involving any SGLT-2 inhibitor compared with any DPP-4 inhibitor (abstract 131-LB). A total of 6 studies met the inclusion criteria, 3 of which provided data ≥52 weeks. The investigators found a greater reduction in
HbA1c with the SGLT-2 inhibitors at ≥52 weeks (difference, -0.11% [-0.20, -0.03%]) but not at ≥26 weeks (difference, -0.07% [-0.18, 0.03%]). SGLT-2 inhibitors were also associated with significantly greater change in weight than the DPP-4 inhibitors: -2.3 kg (-2.7, -2.0) at ≥26 weeks and -2.5 kg (-2.8, -2.1) at ≥52 weeks. Corresponding changes in blood pressure also favored the SGLT-2 inhibitors. Not surprisingly, genital infections were more common with the glucosuric agents (relative risk 3.4 [2.0, 6.0]). Episodes of DKA were not reported. The investigators concluded that the SGLT-2 inhibitors were modestly (we might say minimally) more efficacious than the DPP-4 inhibitors, and associated with better effects on BP and weight, but at the expense of more genital infections. As with all diabetes therapies, individualization is key, in an effort to accentuate the benefits and minimize the adverse effects for each patient.

*In Combination with TZDs?*

The TZD, pioglitazone, is being used less commonly than in the past in T2DM owing to its side effect profile. One reasonably frequent adverse effect, affecting at least 5-10% of patients (more if used concurrently with insulin), is edema. This is believed to be the result of increased sodium retention by the distal nephron. Given that the SGLT-2 inhibitors have an osmotic diuretic (and to some degree natriuretic) effect, some have proposed that these two classes might be an attractive pairing in patients who require combination therapy. Conceivably, the improved heart failure outcomes observed in EMPA-REG might also offset the increase in heart failure hospitalization rates seen with the TZD class. Gautam et al. from India tested this hypothesis in a ‘late-breaking’ poster (abstract 140-LB). The group studied 62 patents who were randomized into two groups (30 study cases versus 32 comparators) who had developed edema on pioglitazone (usually in conjunction with other glucose-lowering drugs).

Study cases were treated with canagliflozin 100 mg OD, and their TZD dose was left unchanged (although other drugs could be adjusted to avoid hypoglycemia). In the comparators, the pioglitazone dose was reduced or the drug was stopped entirely, depending on the severity of the edema. All patients were followed for 4 weeks and their weight and edema grade were tracked. 24 out of 30 (80%) of the study cases demonstrated complete resolution of edema with a mean weight loss of 3.8 kg. In the comparator group, the corresponding figures were 12 out of 32 (37.5%) and -1.6 kg. (p<0.05 for both comparisons). Hypoglycemia was experienced by 2 in the study case group and none of the comparators. Elevated blood glucose was observed in 5 (17%) of the study cases and 8 (25%) comparators. The investigators concluded that combination therapy with pioglitazone and canagliflozin could resolve fluid retention by the former agents. Longer and larger studies are needed to better explore the issue of heart failure. Also, both pioglitazone and canagliflozin have been associated with increased fracture risk, the data being robust with the TZD and only preliminary with the SGLT-2 inhibitor. Nonetheless, this will obviously be a concern moving forward.

*Weighing the Risks and Benefits*

An entire symposium entitled The Good Heart, the Bad Bone, and the Ugly Fat Cell focused on SGLT-2 inhibitors. Sunder Mudaliar, MD from the University of California San Diego initiated the conversation with an overview of the drugs’ effect on blood pressure, body weight, and fat distribution. He reviewed a meta-analysis (27 RCTs, n=12,960) of the effect on blood pressure (Baker WL, et al. J Am Soc Hypertension, 2014). A consistent lowering of SBP (-4 mm Hg) and DBP (-1.6 mm Hg) occurred through all studies. SGLT-2 inhibitors were also associated with significant decreases in body weight. Similar data were observed in a 4-year durability study of dapagliflozin compared with sulfonylureas: sustained blood pressure reduction (3.7 mm Hg)* and weight loss (4.4 kg) were observed in the dapagliflozin group versus glipizide over a 4-year period (Del Prato S, et al. Diabetes Obesity Metabolism, 2015). Additional investigations have demonstrated like results, and in several of these, blood pressure lowering occurred in patients already treated with ACE inhibitors and ARBs. Cherney et al. hypothesized that blood pressure lowering may be due, in part, to improved arterial compliance. In a study of normotensive Type 1 diabetes patients (n=40), administration of empagliflozin for 8 weeks led to a decrease in arterial stiffness as measured by carotid radial pulse waves compared to baseline in addition to the expected lowering of blood glucose, body weight, and blood pressure (Cardiovascular Diabetol, 2014). Based on these and other studies, Dr. Mudaliar suggested that blood pressure lowering is likely due to diuresis and weight loss in the short-term; however, long-term effects may be mediated through renal effects and within the vasculature itself.

Weight loss is often less than what one might predict based on SGLT-2-induced urinary calorie losses. What is now known is that chronic glucosuria induces an adaptive increase in energy intake. Addition of SGLT-2 inhibitors combined with caloric restriction would therefore result in
weight reduction as expected, which has been demonstrated (Ferrannini G, et al. Diabetes Care, 2015). With respect to the fat cell, Mudalir shared data from a 24-week study involving dapagliflozin versus placebo that was extended to 2 years. This study demonstrated that total body weight and body fat mass continued to decline even at the 2-year mark. Additionally, close to 70% of weight loss reduction was attributed to a decline in body fat mass as measured by DEXA (Bollinder J, et al. Diabetes Obesity Metabolism, 2014). In closing, Dr. Mudalir shared a figure recently published by Rajasekera et al. (Figure 14, page 26) that speculated about the mediators of the drug class’ benefits on both the heart and the kidney. David Aguilar, MD, from the Baylor College of Medicine, addressed the benefits and safety of SGLT-2 inhibitors in patients with heart failure. While other diabetes medications have either exacerbated or been neutral on heart failure outcomes, as noted above, empagliflozin therapy has been associated with a 35% relative risk reduction for heart failure.* In a subgroup analysis of EMPA-REG (Fitchett D, et al. Eur Heart J, 2016), it was demonstrated that the CV benefits of reduced heart failure hospitalizations and CV death were consistent in those with and without baseline heart failure. These data suggest that the drug may not only affect the worsening of heart failure but might also prevent its development.*

Naim Maalouf, MD from the University of Texas Southwestern Medical Center in Dallas reviewed the effect of SGLT-2 inhibitors on bone health, suggesting that it might be a direct effect or possibly, incidental. Diabetes itself is an independent risk factor for fracture. The mechanisms for drug-induced fractures are multifaceted including increased fall risk, accelerated bone loss, and/or bone mineral changes. With respect to incidence of fractures, the data are curious. To date, only canagliflozin has been associated with a higher incidence of fractures (6 additional fractures per 1000 patient-years, HR = 1.51). The increased rate occurred in only one (i.e., CANVAS) of nine phase 3 canagliflozin studies of greater than one year duration. One study with dapagliflozin has demonstrated an increased risk of fracture in patients with CKD (Kohan DE, Kidney International, 2014), whereas in non-CKD patients there was no imbalance. The EMPA-REG OUTCOME trial identified no difference in fractures between drug and placebo as well as 17 other RCTs involving empagliflozin. Maalouf then reviewed known evidence that may contribute to potential increased risk including fall rates, bone mineral density (BMD), bone turnover, serum phosphorous, and weight change as a function of decreased BMD (Table 12). His final conclusion was that more research is necessary to better understand this relationship.

Simeon Taylor, MD, PhD from the University of Maryland closed the symposium with a discussion on the risk of DKA with the SGLT-2 inhibitors. He commented that the risk of DKA and the FDA Alert of 5/15/2015 likely caught most practitioners off guard. Yet in hindsight, it may have been predicted. DKA was originally identified when SGLT-2 inhibitors were used off-label for Type 1 diabetes, resulting in lower blood glucose values and subsequent decreases in insulin dose. Patients, as a result, experienced increased ketogenesis. A recent study with canagliflozin in Type 1 diabetes patients demonstrated large increases in serious ketone-related adverse events when compared to placebo (Henry RR, Diabetes Care, 2015). All of the events were associated with precipitating factors (i.e., infection, pump failure or malfunction and/or inappropriate insulin dosing); most occurred early on during therapy (Table 13). The effects in T2DM patients are less well described. However, based on voluntary reports of ketoacidosis occurring in all patients receiving an SGLT-2 inhibitor since the drugs were approved (n=259) versus those who received either saxagliptin or sitagliptin (n=477) and using a denominator of total drug sales for these groups of drugs in that time frame, Taylor estimated a 14-fold increase in likelihood for the SGLT-2 inhibitor class when compared with DPP-4 inhibitors. Based on recent work by Ferrannini et al. (Diabetes 2016), Taylor supports the concept that SGLT-2 inhibitors promote a shift away from glucose oxidation toward lipid oxidation. A direct effect on alpha-cells results in an increase in glucagon secretion, stimulating ketogenesis by the liver. Regardless of the pathogenesis, Taylor closed by urging practitioners to avoid off-label use of SGLT-2 inhibitors in Type 1 diabetes patients. Given the non-glycemic benefits of these drugs, he is hopeful that further research will eventually guide use. In the interim, Taylor advised to avoid using ketonuria as a screening tool or hyperglycemia. He suggested patient education with a close eye toward clinical symptoms such as abdominal pain, nausea, and vomiting being a more practical approach for monitoring.

These and other presentations at this week’s ADA Scientific Sessions in New Orleans underscore the significant interest in this latest glucose-lowering drug category. We hope to learn more about their risks and benefits and where they fit in the overall management of diabetes patients over the next several years. There is indeed cautious optimism, however.

<table>
<thead>
<tr>
<th>Table 12. SGLT-2 Inhibitors and Fractures</th>
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<tbody>
<tr>
<td><strong>Canagliflozin</strong></td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
</tr>
<tr>
<td><strong>Falls</strong></td>
</tr>
<tr>
<td><strong>BMD</strong></td>
</tr>
<tr>
<td><strong>Bone turnover</strong></td>
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<tr>
<td><strong>Serum phosphorous</strong></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
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BMD = bone mineral density; CKD = chronic kidney disease; CTX = carboxy-terminal collagen crosslinks; OC = osteocalcin.

<table>
<thead>
<tr>
<th>Table 13. Ketone-Related Adverse Events (AEs): Canagliflozin v. Placebo</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>(n=117)</td>
</tr>
<tr>
<td><strong>Serious ketone-related AEs</strong></td>
</tr>
<tr>
<td><strong>Serious DKA AEs</strong></td>
</tr>
<tr>
<td><strong>Non-Serious ketone-related AEs</strong></td>
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Metabolic Reproductive Syndrome: PCOS Rebranded

It’s official, the “Metabolic Reproductive Syndrome (MRS)” begins its reign at these Scientific Sessions of the ADA, as announced at a large symposium by experts in the field—Drs. Andrea Dunai, Helena Teede, David Ehrmann, and Richard Legro. For decades the syndrome, known as Polycystic Ovary Syndrome (PCOS), gained recognition as the most common endocrine condition affecting women, and prompted research into underlying etiology, diagnostic criteria, and best practices for management. However, expert opinion from various specialties and countries drove different criteria for diagnosis, including the 1990 NIH criteria, 2003 Rotterdam criteria, and 2006 Androgen Excess Society criteria (Table 14).

Given these struggles to meet consensus over diagnostic criteria, a panel of impartial experts from several specialties gathered at the NIH in 2012 to clarify the benefits and drawbacks of different diagnostic criteria, among other things. The panel concluded that the name PCOS was “a distraction and an impediment to progress”, causing “confusion” and “a barrier to effective education of clinicians and communication with the public and research funders” (https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/pcos).

Table 14. Diagnostic Criteria for PCOS, Per Different Expert Opinion Panels

<table>
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<tbody>
<tr>
<td>Hyperandrogenism AND</td>
<td>2 out of 3 of: Hyperandrogenism</td>
<td>Hyperandrogenism AND</td>
</tr>
<tr>
<td>Oligo/Amenorrhea</td>
<td>Oligo/Amenorrhea</td>
<td>Oligo/Amenorrhea OR</td>
</tr>
<tr>
<td>Polycystic Ovaries</td>
<td>Polycystic Ovaries</td>
<td>Polycystic Ovaries</td>
</tr>
<tr>
<td>Exclusion of other pathology</td>
<td>Exclusion of other pathology</td>
<td>Exclusion of other pathology</td>
</tr>
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</table>

Not only is the name PCOS a misnomer since ovarian “cysts” are in fact arrested follicles, but the presence of these arrested follicles are not required for diagnosis. In addition, the panel cited the use of multiple classification systems “confusing”, delaying “progress in understanding the syndrome”.

In an unprecedented move, potential new names for the syndrome were held to a “vote” by women with PCOS and primary care physicians in Australia, through a cross-sectional survey (Teede et al. J Clin Endocrinol Metab 2014: 99: E107–11). Metabolic Reproductive Syndrome was generally favored over other options of functional female hyperandrogenism, polylollicular ovarian syndrome, and hormonal imbalance syndrome by women with the syndrome and overwhelmingly preferred by physicians.

Rebranding PCOS as MRS appears only the first step in asserting accuracy in the conversation about this common syndrome. However, it remains unclear as to next steps for generating international consensus for diagnostic criteria. Consensus will likely prove difficult since MRS is multifactorial and carries a spectrum of phenotypes and associated clinical consequences including metabolic syndrome, T2DM, subfertility, and endometrial cancer. No doubt this transition in identity will take time to diffuse into our lexicon, especially since even the speakers in this symposium struggled to incorporate the new name MRS into their presentations.

Progress on Insulin Formulations

Several new insulins have been marketed in the US in the past year or two and many more are under investigation. An afternoon symposium dedicated to this topic began with a presentation on inhaled insulin. Dr. Stefano Del Prato from the University of Pisa, Italy chronicled the history of inhaled insulin, identifying the first known aerosolized product documented by M. Gansslen in 1925. Although a reasonable route of delivery, actual commercial availability has been hampered by optimal particle size to ensure bioavailability and devices that are patient friendly. The turning point was in January 2006 when Exubera® was approved in the US and EU. Its approval represented over 16 years of drug development, greater than 50 clinical trials, and over 47,000 patient-months exposure. Deemed non-inferior to injectable insulin in clinical trials, issues such as loss of efficacy as doses were increased over time and safety concerns regarding lung function prompted the manufacturer to withdraw it from the market within the year after approval. Eight years later, another human inhaled insulin (Afrezza®) was approved by the FDA and remains on the market, but sales are not strong.

Dr. Del Prato remarked that the three main issues determining its viability include: (1) clinical advantages versus other formulations; (2) convenience for the patient; and (3) safety. With respect to clinical comparisons, pharmacokinetic profiles relative to other bolus insulins demonstrate faster absorption and higher peak concentrations. Generally deemed to be non-inferior in comparison to subcutaneous insulin, a meta-analysis of 13 trials evaluated several outcome parameters (Pittas AG, et al. Lancet Diabetes Endocrinol., 2015). HbA1c lowering was greater with subcutaneous, yet inhaled demonstrated less weight gain and hypoglycemia. Overall quality of life and patient satisfaction were no different.

Del Prato stated that despite some potential advantages, he considers inhaled insulin non-inferior clinically and is hopeful that more comparative trials will be conducted, particularly when used in combination with basal insulins. Regarding patient convenience, a comparative trial with pre-mixed aspart insulin actually demonstrated no difference in patient preference between inhaled and injectable (Peyrot M, et al. Diabetes Technol Ther, 2011).

Lastly, safety issues persist, such as an increase in cough and effects on pulmonary function. Inhaled insulin is indeed contraindicated in asthma and COPD. Lung cancer was identified in two patients, each with strong smoking history, in clinical trials as well as in 2 additional patients who were non-smokers following approval. The FDA required that the manufacturer complete a 5-year post-marketing surveillance study to assess long-term malignancy. While inhaled insulin may not be a first-line insulin of choice, it is a novel option for those non-smokers without underlying lung disease who are willing to comply with monitoring of pulmonary function.

Wendy Lane, MD of the Mountain Diabetes and Endocrine Center, Asheville, NC reviewed the benefits and limitations of newer, concentrated insulins. Due to the obesity epidemic, average insulin doses are on the rise. Patients who are candidates for concentrated insulins include mainly obese T2DM patients with insulin resistance. For quite some time, U-500 regular insulin was the only concentrated product approved in the US. Then, in 2015, the FDA approved three concentrated formulations: U-300 glargine, U-200 degludec, and U-200 lispro. Dr. Lane identified specific benefits
and limitations associated with each product (Table 15). She shared an algorithm for high-dose insulin unique to her practice site. Based on basal insulin requirements (BIR), the following formulations are chosen: (1) if BIR < 40 units/day, then glargine U-100 or U-300; (2) if BIR 40-60 units/day, then U-200 degludec or U-300 glargine; and (3) if BIR 60-160 units/day, then U-200 degludec.

Dr. Daniel Anderson of MIT, Cambridge, MA provided insights into future ‘smart insulins.’ He reminded the group that we have already made insulins ‘smarter’ from a pharmacokinetic perspective, however, research is on-going to design insulins that are actually glucose-responsive.* Three approaches include chemical modification, encapsulation, and nanotechnology. Use of compounds that reversibly bind to glucose, such as phenylboric acid, is an example of chemical modification. Another approach is to encapsulate insulin in a chemically responsive shell that degrades or swells in response to glucose. Nanoparticle technology that either turns genes off or on to repair or suppress desired genetic targets is under investigation. The goal for diabetes would be to use this technology in the pancreas to stimulate new insulin secretion.

We believe that these changes in insulin formulations should make insulin safer and more accessible to a greater number of patients. Unfortunately, these newer products come at substantial cost and the escalating price of insulin has given all of us practicing diabetology great concern.

### So Many Posters, So Little Time....

#### Cerebral Edema and DKA

Using ICD-9 CM codes, Siwakoti et al. from Memphis, TN, identified adults diagnosed with DKA or hyperosmolar hyperglycemic state (HHS) and co-existing cerebral edema in the Nationwide Inpatient Sample (NIS) database (abstract 1457-P). Patients with other potential causes of cerebral edema (e.g., stroke, CNS infection/abscess, trauma, malignancy) were excluded. Cerebral edema was determined to be an extremely rare complication of DKA/HHS involving just 0.03% (80 of 252,645) of adult hospitalizations. The mean age of cases was 43.9 ± 16.5 years, and approximately half were female (51%) and white (54%). Patients with cerebral edema had an almost 2-fold higher rate of co-morbidity burden as compared to those without cerebral edema (56% vs. 30% with a Charlson/Deyo score of >1), higher overall mortality rate (35% vs. 1.1%), longer length of stay (5.6 vs. 4.2 days), and higher costs of hospitalization ($58,153 vs. $26,675) (each, p < 0.01).

#### Medical Nutrition Therapy

Medical Nutrition Therapy (MNT) plays a central role in diabetes management. Current standards of medical care in diabetes recommend that each patient engages with a registered dietitian (RD) to develop an individualized eating plan. To determine if this is the most effective MNT approach in obesity, Mottalib and colleagues from Boston randomized 37 overweight or obese, insulin-naïve adults with T2DM (age 59 ± 10 years; HbA1c 7.72 ± 0.91%; weight 98.5 ± 22.2 kg, BMI 33.8 ± 6.7 kg/m²) to 1 of 3 different models of MNT for 16 weeks (abstract 759-P). Group A met with an RD to develop individualized meal plans. Group B instead followed a structured plan that included menus book, using a diabetes-specific nutritional formula (DSNF), and kept food logs. Group C was similar to group B but also received weekly phone calls from a RD for nutritional support. Diabetes medications were stable throughout the study unless a participant reported hypoglycemia.

Compared to baseline, HbA1c and body weight did not change in Group A, whereas they decreased significantly in Group B (-0.53 ± 0.43% and -2.6 ± 2.3 kg; each < 0.001) and Group C (-0.58 ± 0.57% and -2.2 ± 2.9 kg; each p < 0.01). These study findings suggest that obese T2DM patients achieve more favorable effects on glycemia and weight when MNT includes a structured meal plan with menus book, using a diabetes-specific nutritional formula, with the logging of food intake, and argues against the more time-consuming individualizing of diet. While provocative, the study is simply too small to make any definitive conclusions. Moreover, the results may have differed if insulin-treated patients had been included.

* The product is not labeled for the use under discussion or the product is still investigational.

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Duration</th>
<th>Maximum Dose/ Injection (units)</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>U-500</td>
<td>30 min</td>
<td>Up to 8 hr</td>
<td>Highly concentrated, Useful in pumps, Sustained glycemic control with minimal weight gain, Pen formulation resolves several medication safety issues</td>
<td>Long duration of action, potential stacking, Pumps are programmed for U-100 insulins, Bolus MUST be 30-60 minutes prior to meals, Onset too long to be useful as correction dose</td>
</tr>
<tr>
<td></td>
<td>U-300</td>
<td>1-6 hr</td>
<td>24-36 hr</td>
<td>Decreased hypoglycemia, Longer duration of action, Slightly more dosing flexibility (dosing window is q 24 ± 3 hours)</td>
<td>Decreased bioavailability (~10% increase in dose for conversion from U-100 to U-300), Small pen size (1.5 ml) supplying 450 units total</td>
</tr>
<tr>
<td>Degludec</td>
<td>U-200</td>
<td>1-9 hr</td>
<td>&gt; 42 hr</td>
<td>Longest duration of action, Large dose per injection, Bioequivalent to degludec U-100 (no dose titration between degludec formulations)</td>
<td>Must down titrate dose (~10%) when converting from other basal insulins, 2 to 3 days to reach steady state, Formulary access/cost</td>
</tr>
<tr>
<td>Lispro</td>
<td>U-200</td>
<td>10-30 min</td>
<td>3-5 hr</td>
<td>Useful when large prandial doses required (decreased volume of MDIs), 3 ml pen size supplying 600 units total</td>
<td>Not yet FDA-approved for pump use</td>
</tr>
</tbody>
</table>

MDI = multiple daily injections.

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Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University, New Haven, Connecticut
1. Which of the following statements about metformin use is *false*?  
   a. Metformin is recommended as first-line treatment for Type 2 diabetes patients.  
   b. Metformin is now FDA approved for use in patients with mild impairment of renal function and in some patients with moderate impairment of renal function.  
   c. Metformin therapy has been associated with renal injury.  
   d. All metformin-treated patients should have B12 levels measured periodically (or be placed on B12 supplements).

2. GLP-1 receptor agonist therapy confers each of the following benefits for patients with Type 2 diabetes, *except _____*.  
   a. glycemic control  
   b. weight loss  
   c. low risk of hypoglycemia  
   d. oral administration

3. On average, HbA1c lowering with basal insulin combined with a GLP-1 receptor agonist is comparable to that achieved with basal insulin combined with prandial insulin in patients with Type 2 diabetes.  
   a. true  
   b. false

4. In the EMPA-REG OUTCOME trial of Type 2 diabetes patients with overt cardiovascular disease (CVD), all of the following outcomes, *except _____*, were observed with the SGLT-2 inhibitor, empagliflozin.  
   a. The primary endpoint, a composite 3-point MACE (major adverse cardiovascular events), comprised of CV death, non-fatal MI, and non-fatal stroke, was statistically significantly reduced (-14%) by empagliflozin versus placebo.  
   b. The risk of cardiovascular mortality was reduced by 38% in patients randomized to empagliflozin versus placebo.  
   c. The risk of heart failure hospitalizations were reduced by 35% in patients randomized to empagliflozin versus placebo.  
   d. As compared to placebo, patients treated with empagliflozin had the same incidence of genitourinary infections.

5. The cardiovascular benefits in EMPA-REG OUTCOME trial were at the expense of a 39% increase in the risk of the incident or worsening nephropathy.  
   a. true  
   b. false

6. In the LEADER outcome trial of Type 2 diabetes patients with CVD (> 50 years old) or with at least 1 risk factor for CVD (> 60 years old), all of the following outcomes, *except _____*, were observed with the GLP-1 receptor agonist, liraglutide.  
   a. The primary endpoint, a composite 3-point MACE (major adverse cardiovascular events), comprised of CV death, non-fatal MI, and non-fatal stroke, was statistically significantly reduced (-13%) by liraglutide versus placebo.  
   b. The statistically significant treatment benefit with liraglutide based on reduction in the primary endpoint was observed in patients with as well as without overt CVD.  
   c. All-cause mortality was significantly reduced (-15%) by liraglutide.  
   d. A statistically significant treatment benefit with liraglutide (versus placebo) was observed based on a 22% reduction in new or worsening nephropathy.

7. Which of the following statements about diabetes and CVD is *false*?  
   a. There is strong evidence that tight glucose control during ACS hospitalizations improves clinical outcomes.  
   b. Higher HbA1c levels correlate with higher heart failure risk, even at minimally elevated levels in the prediabetic range.  
   c. In diabetes patients, albuminuria (micro and macro) is a risk factor for developing preserved ejection fraction heart failure.  
   d. In the Da Qing study of individuals with impaired glucose tolerance at baseline, developing diabetes was associated with a 2-fold higher risk of CVD.

8. According to study results reported at the 2016 ADA Scientific Sessions, 2-day low calorie diet (500-600 calories) with 5 days of habitual eating per week may lead to comparable glycemic effects and weight loss, as compared to a moderate, continuous energy restriction diet.  
   a. true  
   b. false

9. In the Insulin Resistance Intervention after Stroke (IRIS) trial, non-diabetic, insulin-resistant patients with a prior history of stroke or TIA who were assigned to the thiazolidinedione, pioglitazone, experienced a significant reduction in risk of not only atherosclerotic events (-24%), but also developing diabetes (-52%).  
   a. true  
   b. false

10. In the IRIS trial, the risk reduction for developing diabetes was predominately driven by those patients who had normal glucose tolerance at baseline.  
    a. true  
    b. false

11. According to the 2nd Diabetes Surgery Summit, and endorsed by the ADA, metabolic surgery cannot be recommended as an option for obese Type 2 diabetes patients with uncontrolled glycemia.  
    a. true  
    b. false

12. Diabetic ketoacidosis has been reported for Type 1 diabetes patients during treatment with an SGLT-2 inhibitor, but not for those with Type 2 diabetes.  
    a. true  
    b. false

13. Diabetic patients who develop DKA-associated cerebral edema have a 2-fold higher rate of co-morbidity than those who do not develop the complication.  
    a. true  
    b. false

14. Other than a lower HbA1c, each of the following may be expected during treatment with SGLT-2 inhibitors, *except _____*.  
    a. decreased urinary albuminuria  
    b. decreased blood pressure  
    c. weight loss  
    d. increased uric acid

15. Nondiabetic patients who experience post-surgical stress hyperglycemia are at increased risk of post-operative complications.  
    a. true  
    b. false

Questions 16-20. For Type 2 diabetes patients who have uncontrolled glycemia while being treated with metformin, identify the agent that is relatively contraindicated (as dual therapy), given the following patient factors:

16. Elderly woman with history of leg fracture
    a. sulfonylurea  
    b. thiazolidinedione (TZD)  
    c. DPP-4 inhibitor  
    d. SGLT-2 inhibitor  
    e. GLP-1 receptor agonist

17. Woman with frequent genitourinary infections
    a. sulfonylurea  
    b. thiazolidinedione (TZD)  
    c. DPP-4 inhibitor  
    d. SGLT-2 inhibitor  
    e. GLP-1 receptor agonist

18. Patient who often experiences hypoglycemia
    a. sulfonylurea  
    b. thiazolidinedione (TZD)  
    c. DPP-4 inhibitor  
    d. SGLT-2 inhibitor  
    e. GLP-1 receptor agonist

19. Patient with history of gastroparesis
    a. sulfonylurea  
    b. thiazolidinedione (TZD)  
    c. DPP-4 inhibitor  
    d. SGLT-2 inhibitor  
    e. GLP-1 receptor agonist

20. Patient with a history of pancreatitis
    a. sulfonylurea  
    b. thiazolidinedione (TZD)  
    c. DPP-4 inhibitor  
    d. SGLT-2 inhibitor  
    e. GLP-1 receptor agonist
**Diabetes 2016 Evaluation**

**Volume 33**

The post-test and evaluation must be completed **on-line** (not by US mail or fax) at www.cme.yale.edu.

1. **How would you rate Diabetes 2016 for content?**
   a. very relevant to my practice
   b. interesting but not relevant
   c. uninteresting

2. **How would you rate Diabetes 2016 for coverage?**
   a. broad coverage of the most important diabetes-related topics
   b. too focused on “headlines”
   c. too much scientific data

3. **What percentage of the material is new to you?**
   a. 90%
   b. 70%
   c. 50%
   d. 30%
   e. 10%

4. **How would you rate Diabetes 2016 in meeting the educational objectives of the CME program?**
   a. the objectives of CME program were met
   b. some of the program objectives were met
   c. the program content did not satisfy the objectives

5. **Please indicate if specific educational objectives were met (yes/no):**
   a. Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
   b. Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
   c. Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
   d. Implement strategies for the early diagnosis and treatment of diabetes.
   e. Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
   f. Recognize the interrelationship between insulin resistance, hyperglycemia, inflammation, and atherosclerosis in patients with Type 2 diabetes.
   g. Underscore the importance of lifestyle change, exercise, and dietary interventions in the management of diabetes.
   h. Compare the mechanisms of actions of a growing array of oral and injectable pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper evidence-based role in the management of this disease.
   i. Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
   j. Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
   k. Identify unique management issues among special sub-populations of patients with diabetes.
   l. Discuss the impact of diabetes on healthcare systems.

6. **Will you make changes that will benefit patient care as a result of information received?**
   If yes, please describe: ________________________________________________________________

7. **Do you anticipate any barriers to making these changes?**
   If yes, please describe: ________________________________________________________________

8. **Additional comments: ________________________________________________________________

   Thank you for your participation.
Diabetes 2016 Answer Form (Sample Form)
Volume 33

To receive 5.0 AMA PRA Category 1 Credits™, you must successfully complete the test and program evaluation, which must be completed on-line at www.cme.yale.edu. 80% constitutes a passing grade. Term of approval: June 2016 to December 31, 2016.

Diabetes 2016 Evaluation - Volume 33

1. (a) (b) (c) (d)
2. (a) (b) (c) (d)
3. (a) (b)
4. (a) (b) (c) (d)
5. (a) (b)
6. (a) (b) (c) (d)
7. (a) (b) (c)
8. (a) (b)
9. (a) (b)
10. (a) (b)
11. (a) (b)
12. (a) (b)
13. (a) (b)
14. (a) (b) (c) (d)
15. (a) (b)
16. (a) (b) (c) (d) (e)
17. (a) (b) (c) (d) (e)
18. (a) (b) (c) (d) (e)
19. (a) (b) (c) (d) (e)
20. (a) (b) (c) (d) (e)

Please indicate the number of hours actually spent in this educational activity, up to a maximum of 5.0 hours: ____________

Diabetes 2016 Evaluation - Volume 33

1. (a) (b) (c)
2. (a) (b) (c)
3. (a) (b) (c) (d) (e)
4. (a) (b) (c)
5. (a) yes / no (b) yes / no (c) yes / no (d) yes / no (e) yes / no (f) yes / no (g) yes / no (h) yes / no
   (i) yes / no (j) yes / no (k) yes / no (l) yes / no

6. Will you make changes that will benefit patient care as a result of information received? If yes, please describe: ____________

7. Do you anticipate any barriers to making these changes? If yes, please describe: ________________________________

8. Additional comments: ________________________________

This CME program is sponsored by Yale School of Medicine, New Haven, CT.
We hope you enjoyed the 2016 V.3 Diabetes Newsletter.

Please visit the Diabetes Webpage and click on the "Diabetes Online Quiz" button in order to retrieve your certificate.

Click [HERE](http://www.yalecme.org) to be directed to the Yale CME Diabetes Webpage.

Please note: When you begin the quiz, you will be prompted to log into your Yale CME Profile or create an account for our First Time Users.