Volume 34

Highlights from the
52nd Annual Meeting of
the European Association
for the Study of Diabetes

September 12-16, 2016
Munich, Germany

This CME program is supported in part through 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.
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October 2016

Dear Colleague:

Time restraints prevented many of you from attending the 52nd Annual Meeting of the European Association for the Study of Diabetes (EASD) which was held two weeks ago in Munich, Germany. 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 three 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: October 2016 to July 31, 2017.

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.
- 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.

**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 EASD 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 the *Diabetes 2016* monograph, we summarize important new diabetes information that was presented at the 52nd Annual Meeting of the European Association for the Study of Diabetes (EASD) in Munich, Germany.

After more than three decades of essentially negative trials, beneficial cardiovascular (CV) effects have been recently reported for three separate glucose-lowering agents: the SGLT-2 inhibitor empagliflozin* (EMPA-REG OUTCOME) and two GLP-1 receptor agonists, liraglutide* (LEADER) and now semaglutide* (SUSTAIN-6), with results from each of these trials presented at the 2016 EASD annual meeting. These findings add to the favorable effect on CV events suggested in prior years with metformin* *(UKPDS, HOME trial) and the thiazolidinediones, pioglitazone* *(PROactive, IRIS [the latter in patients with prior stroke and insulin resistance, but not diabetes]). Together, taken news from these trials provides encouragement to clinicians and investigators: We can indeed improve CV outcomes in our patients with Type 2 diabetes with glucose-lowering drugs. However, CV benefit appears to stem from the method by which we lower glucose, rather than glucose-lowering itself, or the exact HbA1c level achieved.

In the EMPA-REG OUTCOME trial (7,020 Type 2 diabetes patients with Type 2 diabetes with overt CV complications), presented at last year’s EASD meeting in Stockholm, Sweden, the SGLT-2 inhibitor empagliflozin reduced the risk of the primary outcome of major adverse CV events (MACE) by 14% (p=0.04). Importantly, the major driving factor in this result was an impressive 38% relative risk reduction in CV mortality (and a 32% in all-cause mortality, both p<0.0001). In terms of the other MACE components, non-fatal myocardial infarction (MI) was numerically less frequent and non-fatal stroke was numerically more frequent in the active therapy group, but both differences were not statistically significant. Another surprising effect of empagliflozin was a benefit on heart failure hospitalization, which was reduced by 35% (p=0.002). Subsequently (at the 2016 American Diabetes Association [ADA] Scientific Sessions), EMPA-REG investigators revealed that randomization to empagliflozin was associated with a 39% reduction in the progression of diabetic kidney disease (p<0.001), a composite of persistent macroalbuminuria, doubling of serum creatinine (with eGFR <45 mL/min/1.73 m²), the need for renal replacement therapy, and renal death.

At the 2016 EASD meeting in Munich, Germany, the EMPA-REG trialists reported “One-Year Later” results: The 38% reduction in CV mortality was contributed to by numerical reductions in each sub-category: fatal MI, fatal stroke, fatal heart failure, sudden death, and “other CV deaths” (e.g., unwitnessed, likely sudden deaths), with the latter three contributing the most. Interestingly, the reductions in heart failure hospitalizations were statistically similar in those with (HR=0.75) versus without heart failure (HR=0.59); reductions in CV mortality were also experienced by both those with (HR=0.67) and without heart failure either at baseline or during the trial (HR=0.63.) Finally, a composite outcome representing progression of renal disease was significantly reduced by the SGLT-2 inhibitor (HR=0.61), with most components of the composite contributing to this finding (i.e., new macroalbuminuria: HR=0.62; doubling of serum creatinine: HR=0.56; and the initiation of renal replacement therapy: HR=0.45).

The results of the placebo-controlled LEADER study (9,340 Type 2 diabetes patients aged ≥50 years with ≥1 definitive CV comorbidity; followed for a median of 3.5 years) were initially presented in June at the 2016 ADA Scientific Sessions. Fewer patients randomized to liraglutide, as compared to placebo, experienced the primary MACE outcome (HR=0.87, p<0.001 for noninferiority; p=0.01 for superiority). CV death was reduced in the liraglutide arm (HR=0.78, p=0.007), as was all-cause mortality (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 their point estimates <1.0 indicate a possible beneficial trend and certainly no increased risk. Other benefits from liraglutide in LEADER included a 16% reduced incidence of microvascular events (p=0.016), driven solely by less new or worsening nephropathy (HR=0.78, p=0.003). This composite was, in turn, driven essentially by less persistent macroalbuminuria.

At the EASD meeting, LEADER investigators reported that the expanded MACE outcome, which included coronary revascularization and hospitalization for unstable angina or heart failure, was significantly reduced by 12% in the liraglutide arm; there was no heterogeneity for the overall primary outcome or for heart failure hospitalization when analyzed by heart failure at baseline (Class 2-3 vs. Class 1 or no heart failure); a significant interaction (p=0.01) was noted for baseline renal status for the primary MACE (HR=0.94 for those with eGFR ≥60 mL/min and HR=0.69 for those with eGFR <60 mL/min), suggesting a larger effect size in those with more impaired kidney function. Of note, the cohort of elderly patients with only CV risk factors but no established CV disease appeared to experience no significant CV benefit from liraglutide.

SUSTAIN-6 enrolled ~3,300 Type 2 diabetes with established CV disease or CV risk factors who were randomized to semaglutide or matching placebo and followed for about 2 years. Semaglutide reduced risk of the primary outcome of MACE by 26% (p<0.001 for non-inferiority). In contrast to the LEADER results, however, there appeared to be no effect on CV mortality (HR=0.98), possibly related to SUSTAIN’s shorter duration. Instead, the major effects with semaglutide appeared to be on both non-fatal MI (HR=0.74, p=0.012) and stroke (HR=0.61, p=0.04). There was no effect on heart failure hospitalization. There was little heterogeneity for the primary outcome between various prespecified subgroups including age, race, sex, baseline HbA1c, and renal function. However, the point estimate for the primary outcome was >1.0 in those with heart failure at baseline (HR=1.03) and those using insulin at baseline (HR=1.02). And, the drug appeared to have a neutral effect in those included in the trial on the basis of age ≥60 and CV risk factors as opposed to overt CV disease (HR=1.00).

We are entering a new era in diabetes care. These three recently reported trials demonstrated very clearly that use of at least certain GLP-1 RAs (liraglutide, semaglutide) or certain SGLT-2 inhibitors (empagliflozin) in high-risk patients confers CV benefits on top of standard-of-care. We suspect the findings of these trials will become incorporated into treatment guidelines at some point in the near future.

More details on these and other topics are found in this volume of *Diabetes 2016.*

* The product is not labeled for the use under discussion or the product is still investigational.
Treatment options for patients with Type 2 diabetes have expanded dramatically over the past two decades. There are now 12 individual classes of glucose-lowering medications, each with a unique mechanism of action. Most classes have several choices, most with both generic and brand names, some in combinations with other categories. Clearly, the management of this disease is getting increasingly complex!

The newest type of anti-hyperglycemic medication to join the pharmacopeia for Type 2 diabetes is the sodium-glucose cotransporter (SGLT)-2 inhibitors. Currently available members of this category are canagliflozin, dapagliflozin, and empagliflozin. These drugs reduce plasma glucose concentrations by augmenting urinary glucose excretion via the inactivation of the major transporter that serves to reclaim the vast majority of glucose in the glomerular filtrate. The agents also have modest beneficial effects on body weight (−2 kg) and blood pressure (−4/−2 mmHg), the latter likely owing to their mildly natriuretic effect. Adverse effects include polyuria and the risk of dehydration. Also, the drugs are associated with a significant increase in genital mycotic infections, and in some studies, increased urinary tract infections. Recently, an additional potential risk has emerged: diabetic ketoacidosis (DKA). Originally noted in patients with Type 1 diabetes who were using the medicines in an off-label fashion, cases are now being reported, albeit rarely, in those with Type 2 diabetes as well. DKA may stem from SGLT-2 inhibitors’ tendency to increase both fat oxidation and glucagon secretion, combined with a reduction in baseline insulin doses due to overall improved glycemia. Interestingly, some patients who develop DKA after SGLT-2 inhibition do so with just mild hyperglycemia—so-called “euglycemic DKA.” This may delay its recognition in the acutely ill.

Excitement about the drug category began with the EMPA-REG OUTCOME trial results, presented at last year’s EASD meeting in Stockholm, Sweden. In that cardiovascular (CV) outcome trial, the SGLT-2 inhibitor empagliflozin reduced the risk of the primary outcome of major adverse CV events (MACE) by 14% (p=0.04). Importantly, the major driving factor in this result was an impressive 38% relative risk reduction (RRR) in CV mortality (and a 32% in all-cause mortality, both p<0.0001). In terms of the other MACE components, non-fatal myocardial infarction (MI) was less frequent and non-fatal stroke was more frequent in the active therapy group, but both differences were not statistically significant. Another surprising effect of empagliflozin was a benefit on heart failure hospitalization, which was reduced by 35% (p=0.002). A key observation from the EMPA-REG trial was the early diversion of the event curves for both CV mortality as well as heart failure hospitalization, suggesting an early hemodynamic effect and less likely a benefit mediated through reducing atherosclerosis.

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Benefits in Kidney Disease

Heerspink and international collaborators suggested that SGLT-2 inhibitors confer renoprotection, basing this conclusion on data from canagliflozin clinical trials that showed a reduction in albuminuria when used in patients with diabetic nephropathy (abstract 53). They conducted a post-hoc analysis of a Phase 3 clinical trial involving 1,450 patients with Type 2 diabetes randomized to canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride 6 to 8 mg. The endpoints examined were the change in estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (UACR) over a period of 2 years.

The mean HbA1c reductions in all three groups were similar both at 12 months (0.81%, 0.82%, and 0.93% for glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg, respectively) and 24 months (0.55%, 0.65%, 0.74%, respectively). In contrast, the annual change in eGFR decline was
3.3 mL/min/1.73 m² (95% confidence interval [CI], 2.8, 3.8) with glimepiride, and 0.5 mL/min/1.73 m² (0.0, 1.0) and 0.9 mL/min/1.73 m² (0.4, 1.4) with the low and high canagliflozin doses, respectively (p < 0.01 for each vs. the sulfonylurea) (Figure 1). Results were similar in those with and without prevalent albuminuria (>30 mcg/mg creatinine) at baseline. In the albuminuric subgroup, UACR was reduced significantly by 100 mg (-31.7%) and 300 mg (-49.3%) of canagliflozin, as compared to glimepiride. The between-groups differences in UACR persisted after adjustments for on-trial changes in HBAlc, blood pressure, and body weight. The investigators concluded that canagliflozin slows the progression of renal disease as compared with glimepiride. Of course, this may be an over-reaching conclusion, since albumin excretion is just a marker of renal disease and its diminution is not necessarily proof of any benefit on decline in GFR. The changes found in GFR, while statistically significant, are small, and longer-term results are needed.

As reported in this newsletter in June (Diabetes 2016 Volume 33, Issue 4), however, from the 2016 Scientific Sessions of the American Diabetes Association in New Orleans, the EMPA-REG investigators revealed more definitive data on renoprotection. In that study, randomization to empagliflozin (10 or 25 mg) was associated with a 39% reduction in the progression of diabetic kidney disease (p < 0.001), a composite of persistent macroalbuminuria, doubling of serum creatinine (with eGFR < 45 mL/min/1.73 m²), the need for renal replacement therapy, and renal death. Some nephrology experts have proposed that this benefit may simply be explained by a reduction in glomerular baro-trauma from afferent arteriolar vasoconstriction, due to tubulo-glomerular feedback (TGF) from the macula densa, which senses increased sodium delivery from the proximal nephron. (See recent review by Heerspink HJ, et al. Circulation 2016; 134:752-72).

Evaluating Risks

Canagliflozin has recently been associated with a small increase in fracture rates. It remains unclear if this effect is real, and, if so, whether it results from any effect of SGLT-2 inhibition on renal calcium or phosphate handling, bone mineral density, or the propensity to fall, the latter perhaps related to hyptensive episodes. Kohler and German colleagues conducted a pooled safety analysis of 15 empagliflozin trials from the drug’s Phase I-III program, including 4 extension trials (abstract 49). Bone fracture data were collected from investigators’ reports of adverse events. A total of 4221, 4196, and 4203 patients received empagliflozin 10 mg or 25 mg or placebo, respectively, with a median exposure of between 650-700 days. Bone fracture adverse events were reported in 119 (2.8%), 105 (2.5%), and 123 (2.9%) patients across the three randomized groups. This corresponded to nearly identical incident rates of 1.55, 1.36, and 1.69/100 patient-years, respectively. There were also no detectible changes from baseline in calcium or phosphate levels in any of the groups. These data are encouraging, and it will be important to conduct similar analyses with the other SGLT-2 inhibitors. In addition, safety data following more long-term exposure are needed.

Asth noted above, DKA is an emerging concern with this drug class. The etiopathogenesis of this complication also remains incompletely understood. Originally it was thought that episodes occurred simply because of overly aggressive down-titration of insulin doses in patients using the drugs off-label in Type 1 diabetes. While this is certainly partially to blame, episodes in Type 2 diabetes suggest other mechanisms may be at play. For example, SGLT-2 inhibition has been shown to activate fat oxidation, providing more fuel (free fatty acids) for ketogenesis. The pancreatic alpha cell’s response to SGLT-2 inhibition is to increase glucagon secretion. This may promote hepatic beta-hydroxybutyrate production. Finally, SGLT-2 inhibition may also decrease urinary ketone clearance.

Ongoing controversy regarding the physiology of ketogenesis with these agents stimulated a group from the University of Texas, San Antonio, led by Solis-Herrera, to conduct a small mechanistic study involving 18 patients who were randomized to 10 mg of dapagliflozin versus matching placebo for two weeks (abstract 51). Before and after therapy, the study patients underwent euglycemic hyperinsulinemic clamps with tritiated glucose (to measure hepatic glucose production), and indirect calorimetry (to assess oxidation). Despite being small, the two groups were well matched for age, BMI, and HBAlc. Dapagliflozin therapy decreased fasting plasma glucose (FPG) from 167±13 to 128±6 mg/dL and also increased insulin-stimulated glucose disposal during the clamp by 36% as compared with placebo (p < 0.01). This was mainly on the basis of an increase in non-oxidative glucose metabolism, which was augmented from 2.74±0.59 to 4.74±0.51 mg/kg/minute (p < 0.001 vs. baseline and p < 0.01 vs. placebo). Dapagliflozin did not affect circulating free fatty acid concentrations, but lipid oxidation was mildly increased from 2.48±0.34 to 2.82±0.12 mg/kg/minute (p < 0.05 vs. baseline). In contrast, lipid oxidation was slightly decreased in the placebo patients (2.06±0.15 to 1.89±0.10 mg/kg/min, p < 0.05 vs. dapagliflozin). Dapagliflozin also prominently increased the fasting glucagon:insulin ratio, from 14±5 to 35±11 (p < 0.01 vs. baseline and placebo). Finally, the fasting plasma ketone concentration increased from 0.05±0.01 to 0.2±0.01 mmol/L in the dapagliflozin group (p < 0.01 vs. baseline); there was no change in the placebo group (0.09±0.02 mmol/L, p < 0.01 vs. dapagliflozin). The investigators concluded that the SGLT-2 inhibitor resulted in a shift in substrate oxidation from glucose to lipids, and this was associated with a marked increase in the glucagon:insulin ratio. They felt that these metabolic changes provide a clear basis for the increased risk of DKA, especially in the setting of insulinopenia (even in Type 2 diabetes patients), as well as following strenuous exercise, ethanol ingestion, or severe medical or surgical stress.

How common is DKA with this class?
Lund and a German group examined data from Phase I-III studies in the empagliflozin program (abstract 50). A total of 18 studies were included in the analysis, all involving patients with Type 2 diabetes. DKA episodes were tracked on the basis of investigators reporting of adverse events, which were searched using global terms consistent with DKA. There were a total of 8,368, 11,017, and 10,472 patient-years in the empagliflozin 10 mg and 25 mg and comparator groups, respectively. DKA occurred at a very low and equivalent level in all groups (Table 1) in the range of 0.02–0.06 events per 100 patient-years of therapy. Despite these encouraging findings, we note that a recent report from a canagliflozin study involving patients with Type 1 diabetes found a DKA rate of 6.0% with the highest dose (300 mg), with any ketone-related adverse event occurring in 9.4% of participants on this dose (Henry RR et al, Diabetes Care 2015 Oct; dc151730. http://dx.doi.org/10.2337/dc15-1730).

So, until further study, this drug class should be considered only in patients with Type 2 diabetes.

**Combination Therapy?**

One of the additional benefits of SGLT-2 inhibitors is weight loss, which is modest, averaging about 2 kg in most studies. Another anti-hyperglycemic drug category, the GLP-1 receptor agonists also decrease body weight,* perhaps to a somewhat greater degree. The use of these drugs in combination has been proposed as an ideal dual therapy in obese patients with Type 2 diabetes. However, the most recent American Diabetes Association (ADA)-European Association for the Study of Diabetes (EASD) treatment guidelines do not endorse this combination, due to lack of clinical trial evidence of either efficacy or safety. At this week’s meeting in Munich, two small studies were presented that explored dual SGLT-2 inhibition-GLP-1 receptor activation, one in patients with and one in patients without diabetes.

Pappas et al. from Greece evaluated the effect of a dapagliflozin-liraglutide combination over 6 months in 54 patients with Type 2 diabetes (mean age 55 ± 10 years, mean disease duration 7.5 ± 4.0 years [abstract 715]). In this non-randomized study, 33 patients (61%) had the combination added to their background anti-hyperglycemic therapy (Group A) whereas 21 patients (39%) had dapagliflozin added to a baseline regimen that already included liraglutide (Group B). HbA1c, weight, and blood pressure were tracked over time. Overall, about 3 out of 4 patients were using metformin and half were on insulin. At baseline, the mean HbA1c was 8.6 ± 1.4%. After 6 months, the mean HbA1c levels in Group A and B were reduced by 1.96 ± 0.82% and 1.40 ± 0.68%, respectively (between groups, p=0.033). Weight loss was also greater in Group A (6.7 ± 2.6 kg versus 4.6 ± 2.1 kg, p=0.046). Reductions in both systolic (10 ± 5 versus 8 ± 3 mmHg, p=0.211) and diastolic blood pressure (4 ± 2 versus 4 ± 2 mmHg, p=0.287) were not significantly different between the groups. It was concluded that the dapagliflozin-liraglutide combination results in significant improvements in glycemia, body weight, and blood pressure. The investigators suggested that simultaneous initiation of the duo leads to a stronger effect than sequential therapy. We would point out, however, that this finding may just as easily relate to differences in baseline characteristics given the study’s non-randomized design.

Eriksson and Swedish collaborators conducted a randomized clinical trial of dapagliflozin with another GLP-1 receptor agonist, once weekly exenatide (abstract 700). As previously reported by this group at the ADA Scientific Sessions 2015, New Orleans, LA, the combination resulted in an approximate 4 kg weight loss as compared to placebo after 24 weeks in 50 obese, non-diabetic patients. In Munich, the investigators presented the results of a 52-week open-label extension of this trial to which both patients initially assigned to dual therapy or to placebo were invited. All patients were assessed anthropometrically and biochemically, with an oral glucose tolerance test (OGTT) additionally performed in those initially randomized to dapagliflozin/exenatide. Thirty-eight patients entered the extension but 9 did not complete due to nonadherence or adverse effects. The placebo group (n=15 completing 52 weeks) lost 4.7 kg between weeks 24 and 52 (p<0.01 versus week 24 weight), with the original combination therapy group (n=14) losing an additional 1.1 kg for a total loss of 5.9 kg at one year (p<0.05 versus baseline). Combination therapy also resulted in statistically significant reductions in systolic blood pressure, as well as in HbA1c, fasting, and 2-hour OGTT glucose (but, again, the patients did not have diabetes). The investigators suggested that this novel combination therapy might be a future strategy to achieve and maintain weight loss in obese patients. While an interesting concept, the losses to follow-up limit the findings from this study, which is essentially a ‘completers analysis’ and thus has major inherent biases.

Moreover, currently the combination of a SGLT-2 inhibitor and a GLP-1 receptor agonist is an extremely expensive one, approaching or even exceeding $1,000/month in most areas of the country, depending on brand and dose. So, even in a diabetic population, the benefits would have to be large to be worth such an investment. We would also add that, since members of both classes have now been associated with cardiac benefits (liraglutide in LEADER and empagliflozin in EMPA-REG OUTCOME), a long-term combination trial should be considered to see if dual therapy could further reduce CV events.*

Erondu et al. from the US and Belgium tested another combination for weight loss involving an SGLT-2 inhibitor (abstract 76)—canagliflozin with the appetite suppressant, phentermine—in overweight and obese individuals.

### Table 1. Diabetic Ketoacidosis in Type 2 Diabetes Patients

<table>
<thead>
<tr>
<th></th>
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<td>Any DKA adverse event</td>
<td>5 (0.1)</td>
<td>0.06</td>
<td>2 (&lt;0.1)</td>
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<td>Serious DKA adverse event</td>
<td>5 (0.1)</td>
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DKA = diabetic ketoacidosis.

Data from patients treated with ≥1 dose of study drug.

*Adverse events reported as serious adverse events by investigator.

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delaying onset of absorption. BioChaperone™ is a single subcutaneous injection) at the start of a
Lispro or the original insulin lispro (0.2 units/kg new patented technology; a small oligosaccharide
cytotoc self-associate to hexamers and dimers, molecule used as an excipient binds with lispro,
original formulation that has been available for many years (abstract 7). Insulinshave a tendency
to self-associate with hexamers and dimers, facilitating even faster dissociation and absorp-
tion once administered subcutaneously. Lispro*, an ultra-rapid formulation of lispro, the
newer basal formulations as well as differing methods of titration. Within the mealtime insulin
group, two new “ultra-fast” agents are currently under investigation, both modified versions of cur-
rently used products, insulins lispro and aspart.

**Insulin Analogs**

The rapid-acting (or mealtime) and basal insulin analogs have been available for nearly 20
years and are now integral to the management of many patients with diabetes. Several presenta-
tions addressed the comparative efficacy and safety of newer basal formulations as well as differing
methods of titration. Within the mealtime insulin group, two new “ultra-fast” agents are currently
under investigation, both modified versions of currently used products, insulins lispro and aspart.

**Progress on Prandials**

Heise, representing colleagues from Germany and France, presented data on BioChaperone
Lispro,* an ultra-rapid formulation of lispro, the original formulation that has been available for
many years (abstract 7). Insulins have a tendency to self-associate with hexamers and dimers, delaying onset of absorption. BioChaperone™ is a new patented technology; a small oligosaccharide molecule used as an excipient binds with lispro, facilitating even faster dissociation and absorption once administered subcutaneously.

In a double-blind, cross-over trial, 38 patients with Type 1 diabetes received BioChaperone
Lispro or the original insulin lispro (0.2 units/kg single subcutaneous injection) at the start of a
standardized liquid meal (600 kcal; 80 g carbohydrates; 25 g proteins; 20 g fat). Insulin exposure
and postprandial blood glucose values were measured, with baseline blood glucose controlled to 100
mg/dL utilizing IV insulin (glulisine) or glucose; no basal insulin was permitted. Early insulin exposure
was significantly higher in the BioChaperone group as compared to the lispro group. The area-
under-the-curve (AUC) mean ratio of measurable

<table>
<thead>
<tr>
<th>Figure 2. Change in Body Weight Over 26 Weeks</th>
</tr>
</thead>
</table>
| ![Graph](image)

In summary, there is cautious optimism about this latest category of glucose-lowering
agents with evident CV and renal benefits, at least with empagliflozin. Whether these benefits
will extend to the other members of the class is not clear, but we should have data from
long-term outcome trials with both canagliflozin (CANVAS, CANVAS-R, and CREDENCE) and
dapagliflozin (DECLARE) over the next 1-2 years.

<table>
<thead>
<tr>
<th>Figure 3. Mean Blood Glucose Values Following Mealtime BioChaperone Lispro and Insulin Lispro</th>
</tr>
</thead>
</table>
| ![Graph](image)
group: $T_{0.5} \text{max early}$, 19 vs. 30 minutes, ratio 0.63 (0.57, 0.71); $T_{0.5} \text{max late}$, 142 vs. 167 minutes, ratio 0.85 (0.79, 0.91); and $T_{\text{max}}$, 49 vs. 65 minutes, ratio 0.75 (0.69, 0.83). Lastly and not surprisingly, postprandial blood glucose values favored the faster-acting lispro (Figure 3), with a 61% decrease in blood glucose excursions over the first two hours. Injections were well tolerated and the number of hypoglycemic events did not differ between groups. Heise stated that “faster in and faster out” insulin may prove to be the next step toward achieving a closer profile to physiologic insulin.

In a more clinically focused study, Russell-Jones and international colleagues presented data from ONSET-1, a comparative trial between faster-acting aspart and the original insulin aspart in patients with Type 1 diabetes (abstract 9). The faster aspart uses additional excipients to enhance absorption. Following an 8-week run-in period, patients were randomized to receive double-blind faster aspart (n=381) or aspart (n=380) at mealtime or open-label faster aspart (n=382) 20 minutes post-meal. Insulin detemir was the basal insulin for all patients. The primary endpoint was change in baseline HbA1c at 26 weeks (Figure 4). Pre- and post-trial postprandial glucose values were also measured following a standardized liquid meal (80 g carbohydrate). Change in HbA1c from baseline was significantly greater in the faster aspart at mealtime group versus the mealtime aspart group (estimated treatment difference [ETD]: -0.15% [95% CI: -0.23, -0.07%]). The change from HbA1c baseline was similar between post-meal faster aspart and mealtime aspart (ETD: 0.04% [-0.04, 0.12%]). Two-hour postprandial glucose also favored faster mealtime aspart when compared with aspart (ETD: -12.1 mg/dL [-23.2, -0.7 mg/dL]). Each treatment arm was similar with respect to weight gain (<1 kg), hypoglycemic episodes, and overall tolerability.

From these data, the investigators concluded that faster aspart provides a potentially relevant treatment advance in Type 1 diabetes both from the perspective of a statistically significant reduction change in HbA1c from baseline when faster aspart is administered at mealtime as well as its non-inferiority to insulin aspart when dosed post-meal. While the data are clearly statistically better for this new formulation of aspart, one might ponder as to whether such a small advantage in HbA1c is clinically meaningful. The post-meal issue may offer some added flexibility to patients. However, the likely higher cost of this newer formulation would need to be better justified, in our opinion. Certainly, if the developers are able to demonstrate a measurable benefit on hypoglycemic episodes as well, that would be more convincing.

**Basal-Bonus?**

Options for basal insulin analogs have increased over the past two years including the introduction of insulin degludec and concentrated forms of both degludec (U-200) and insulin glargine (U-300). The comparative safety and effectiveness of these formulations have not been fully elucidated. For this reason, Tsapas et al. from the UK and Greece conducted a meta-analysis of 29 randomized, controlled trials (duration 12 weeks or greater) in adult patients with Type 2 diabetes (n=14,268) (abstract 841). Eight different basal insulins were assessed: degludec, degludec 3 times weekly, degludec-200, detemir, glargine, glargine-300, neutral protamine lispro, and the still investigational LY2963016. With respect to reductions in HbA1c, glargine and glargine-300 resulted in marginally significant decreases when compared with detemir and degludec. The differences were deemed not clinically relevant by the investigators, however. Body weight did not differ between treatment groups with the sole exception of a slight reduction associated with insulin detemir (weighted mean difference ranging from -1.54 to -0.78 kg). Despite lack of any enhanced glucose-lowering efficacy, however, glargine-300 and degludec were associated with a lower incidence of nocturnal hypoglycemia. Given the modest differences, however, the investigators urged practitioners to consider costs and patient preferences when selecting and optimizing insulin regimens.

In another meta-analysis, Philis-Tsimikas and international co-investigators evaluated hypoglycemia rates in eight phase 3 trials comparing insulin degludec (n=3454) and insulin glargine (n=1709), both U-100, in patients with Type 1 (2 trials) and Type 2 (6 trials) diabetes (abstract 888). Rates were analyzed with a negative binomial regression model on patient level data and reported for the total study period as well as a maintenance period defined as 16 weeks to end of study (up to 2 years). In both Type 1 and Type 2 diabetes patients, the degludec group showed lower (p<0.05) rates of confirmed nocturnal (12 AM-6 AM) hypoglycemia (<56 mg/dL). With respect to overall confirmed hypoglycemia, rates favored degludec in patients with Type 2 diabetes (p<0.05), but were not statistically significantly different between degludec and glargine in those with Type 1 diabetes.

**Data from two clinical trial programs (BEGIN and EDITION)** were utilized to assess comparative efficacy between insulin degludec, insulin glargine U-100, and insulin glargine U-300. The populations within these trials represent a diverse group of adult patients with Type 2 diabetes on basal-bolus or basal-oral therapy as well as those who were insulin naïve. Roussel and co-investigators from France, Germany, and the US compared HbA1c and FPG values and hypoglycemia rates in 2 trial-level meta-analyses (abstract 914). In the BEGIN trials (degludec vs. glargine U-100), the glargine arms demonstrated a very small, but statistically significantly greater reduction in HbA1c (LS mean difference = 0.09 [0.01, 0.18]; p<0.024), whereas the degludec arms demonstrated an equally modest greater reduction in FPG (estimated LS mean difference = -6.3 [-9.9, -2.7] mg/dL; p<0.001). In the EDITION studies (glargine U-100 versus U-300), reduction in HbA1c and FPG were comparable between the two glargine arms. When evaluating hypoglycemic events (risk of $\geq$1 confirmed <56 mg/dL) or severe hypoglycemia, degludec and glargine U-100 were comparable over a 24-hour period.
However, the risk was lower with degludec during overnight hours (estimated RR 0.79 [0.66, 0.94], p=0.008). When glargine U-300 and U-100 were compared, glargine U-300 demonstrated a significantly decreased risk of overall hypoglycemia both during the entire 24-hour period (estimated RR 0.89 [0.83, 0.95]; p<0.001) and overnight (estimated RR 0.74 [0.65, 0.83]; p<0.001). The risk was comparable between degludec and glargine U-300, however, when each was compared with glargine U-100. The investigators acknowledged that direct, head-to-head comparisons between degludec and glargine U-300 are now needed.

**Mandate to Titrate**

Once a basal insulin is chosen, how does one optimally titrate to achieve glycemic control? This was the topic addressed in several poster presentations including an evaluation of algorithms by Porcellati et al. of Italy (abstract 864). The researchers evaluated two methods: (1) weekly evening adjustment based on mean FPG values over the previous six days; and (2) every 2 week adjustments based on difference between bedtime and next morning fasting glucose on days when the post-dinner glucose level was at target (100-130 mg/dL) after proper titration of the evening prandial insulin (Table 2).

Patients with Type 2 diabetes (n=212; mean age 62.3 years; BMI 34.2 kg/m^2; HbA1c 8.4%; insulin naïve 37%; prior basal insulin dose 57.2 units) were randomized to either algorithm; HbA1c, FPG, and hypoglycemia were evaluated in parallel group design after three months. Greater decreases in HbA1c values occurred with the second algorithm (7.6±0.9% vs 7.4±0.4% for EDITION and 70.0±43.1 units for EDITION). Mean change in body weight from baseline was 0.41 kg and 0.15 kg for INSIGHT and EDITION, respectively. Based on these findings, self-titration with glargine U-300 using the INSIGHT protocol appears to be effective and comparable to the one implemented by clinicians in EDITION.

### Table 2. Algorithms for Insulin Glargine U-100 Titration

<table>
<thead>
<tr>
<th>Algorithm #1*</th>
<th>Change in Glargine Dose (Units)</th>
<th>Algorithm #2†</th>
<th>Change in Glargine Dose (Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>131-150</td>
<td>+1</td>
<td>≥ +21 to +30</td>
<td>+1/+2</td>
</tr>
<tr>
<td>100-130</td>
<td>0</td>
<td>+11 to +20</td>
<td>0 / +1</td>
</tr>
<tr>
<td>90-99</td>
<td>-1</td>
<td>-10 to +10</td>
<td>0</td>
</tr>
<tr>
<td>&lt;80</td>
<td>-2</td>
<td>-11 to -20</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ -21</td>
<td>-2</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose

*Weekly mean fasting plasma glucose values; weekly titration
† Difference between bedtime blood glucose and next morning FPG on days with post-dinner glucose target (100-130 mg/dL) with optimized evening prandial insulin; every 2 week titration

From the health care professional perspective, barriers for self-titrating patients included: fear of hypo-glycemia (74%) and low patient involvement/motivation (63%). From this survey, the investigators suggested that health care providers prefer a slower, safer approach to titration using higher glucose targets as a means to avoid hypoglycemia. Patients are less concerned about hypoglycemia and more about the time required to attain target. They suggested that patients needed ongoing encouragement as their insulin dose is titrated.

Insulin management has certainly become easier with the advent of insulin analogues with more physiological activity profiles. The value added by the newer insulins are modest, but the lower rates of hypoglycemia with newer and concentrated basal formulations are potentially important. We would not encourage, however, blindly switching to these newer and often costlier products in patients already doing well on their established basal insulins. As noted by several presenters this week, after initiation of basal insulin, it must be titrated either by the clinician or by the patient to achieve HbA1c targets.

*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 School of Medicine
New Haven, Connecticut
Cognitive decline was at the forefront of a large symposium at the 2016 EASD meeting, providing a clear summary of recent evidence for risk assessment in our patients with diabetes. The known association between diabetes and dementia is especially concerning given the increased prevalence of diabetes and our aging population. Moreover, modern intensive risk management to prevent cardiovascular disease will allow more of our diabetic patients to live longer. Unfortunately, declining cognition is an increasingly common and important complication to address. Yet, much work still needs to be done in understanding its pathogenesis and risk factors. Since we do not yet have adequate treatments to reverse dementia, prevention is likely to be the best tool for the foreseeable future.

Dr. Geert Jan Biessels from the Brain Center in Rudolf Magnus, Netherlands provided data from a meta-analysis showing that people with diabetes have a higher relative risk for dementia of 1.73 (95% CI: 1.65, 1.82), independent of other dementia risk factors. It is estimated that 1 in 10-15 dementia cases is attributable to diabetes solely. The relative risk increases to 2.3 (95% CI: 1.9, 2.7) when vascular dementia is specifically examined (Biessels, *Lancet Neurology* 2006;5(1): 64-74). Importantly, post-mortem neuropathological assessment has shown that diabetes is not associated with the classical findings of Alzheimer’s disease, such as amyloid plaques and neurofibrillary tangles. Since diabetes is already a known risk factor for atherosclerosis, it is not surprising that dementia in this population is predominantly vascular dementia.

Importantly, Dr. Biessels carefully delineated that another form of cognitive impairment also occurs in people with diabetes—more subtle and with earlier onset. He and other investigators found that people with diabetes have, on average, lower executive function, learning and memory, and processing speed than non-diabetic individuals (Van den Berg *et al.*, *Diabetologia* 2010;53(1):58-65). For example, the performance range within the verbal memory domain was shifted negatively by about 10% when diabetes coexists, relative to an age-matched general population (Palta *et al.*, *J Internat Neuropsych Soc* 2014;201:278-91). Other neuropsychological parameters such as intelligence, language, and concentration seem to be unaffected. These impairments are separate and distinct from the vascular dementia discussed above, and, importantly, do not represent a continuum of disease. They can be observed in any patient with diabetes, independent of age, and data suggests that they may actually emerge in the prediabetic state (Biessels *et al*. *Lancet Diabetes & Endocrinology* 2014;2(3):246-56).

The pathogenesis of these cognitive changes is not clearly understood, and gaining an understanding is difficult in clinical studies since so many confounders exist. However, Dr. Jens Bruning from Cologne, Germany hypothesized that cognitive dysfunction may occur due to decreased glucose uptake by the brain related to insulin-resistance of vascular endothelial cells in the brain. He used several animal models to demonstrate that high-fat feeding promotes a decrease in the number of GLUT1 glucose transporters at the blood-brain barrier. Fewer GLUT1 resulted in a significant decrease in brain glucose uptake in mice. This model gives insight into a particular defect that may be occurring in the setting of insulin resistance. However, as Dr. Bruning noted, most likely this diabetes-related cognitive decline is multi-factorial (Figure 5).

Neuroimaging techniques provide insights into structural changes in the brain that occur more frequently in people with diabetes. Using MRI, Mankovsky and colleagues from the Netherlands compared the cerebral structure of 93 patients with Type 2 diabetes without history of prior cerebrovascular accident (mean age 62 years, diabetes duration ~10 years, BMI 33 kg/m², HbA1c 8.1%) to that of 18 controls (mean age 60 years, BMI 29 kg/m²) (abstract 254). Mean total brain volume (TBV, 78.8±2.13 vs. 81.3±1.98%), white matter volume (WMV, 43.2±1.34 vs. 43.7±1.04%), and gray matter volume (35.4±2.25 vs. 37.5±2.02%) were lower
Figure 5. Potential Mediators of Cognitive Impairment in Patients with Type 2 Diabetes Mellitus

Dr. Mark Strachan from the United Kingdom assessed risk factors for dementia in the ongoing Edinburgh Type 2 Diabetes Study. He and colleagues followed 828 people of mean age 68 ± 4 years, who had diabetes for a mean duration of 6 (3-11) years, and were predominantly controlled on oral agents (83.7%) with a mean HbA1c of 7.4%. Within this cohort, 60% had never-smoked and 35% had a history of cardiovascular disease. Each subject underwent testing for reasoning, speed, memory, and spatial cognition at baseline, and at 4 and 10 years. The 10-year data are currently under evaluation but data at 4 years has shown that the cohort, overall, had a subtle, yet statistically significant decline in composite neurological scoring, relative to baseline. While there was a large spectrum of cognition scoring within the group, the data may be underestimating the overall decline since the non-attenders at 4 years had significantly lower composite scores at baseline as compared to those who attended the 4-year follow-up. The factors most associated with cognitive decline included baseline HbA1c (effect size -0.10 [p=0.005]) and smoking history (-0.14 [p<0.001]), with, interestingly, blood pressure or cholesterol showing no association (Feinkohl et al., Diabetologia 2015;58:1637-45). History of cerebrovascular accident was associated with greater cognitive decline, but coronary heart disease history was not, after adjustment for age, sex, HbA1c, duration of diabetes mellitus, blood pressure, and cholesterol. Elevated inflammatory mediators, particularly interleukin 6, were also linked with decline, after adjustments. Overall, however, the contribution of HbA1c, smoking history, and inflammation together was estimated as less than 10%.

Since glycemic control is an important modifiable risk factor, Dr. Strachen noted that a study of dementia incidence in the ACCORD study diabetes population found that intensive glycemic therapy to a goal of 6.5% did not reduce dementia incidence (Launer et al., Lancet Neurology 2011;10(11) 969-77). However, the greater incidence and frequency of hypoglycemia in the intensively-treated cohort may have contributed to cognitive decline, in spite of any potential beneficial effect of a lower HbA1c. In the Edinburgh study, participants with the lowest tertile for neurocognitive scoring were twice as likely to experience severe hypoglycemia over the 4 years than those in the highest tertile (Feinkohl et al., Diabetes Care 2014;37:507-15). Dr. Strachen implied that these data have implications for preferring medications, where possible, that do not lead to hypoglycemia.

In summary, people with diabetes are at an increased risk of both cognitive decline throughout the course of their condition, as well as dementia as they age. Both hyperglycemia and hypoglycemia have been implicated, along with underlying intrinsic factors related to brain metabolism. We need more studies on the pathogenesis of diabetes-related cognitive changes so that we can offer better prevention. Promoting good glycemic control and careful avoidance of hypoglycemia may be our best opportunities for prevention beyond the traditional therapies for CV risk modification.

Newer Strategies to Attaining Glycemic Control

In a well-attended symposium on Wednesday morning, entitled “New Paths to Tight Glycemic Control”, three European experts presented their thoughts about optimal strategies for the management of Type 2 diabetes, in the face of a growing array of glucose-lowering therapies.

Leading off the session was Prof. Jochen Seufert from the University Hospital of Freiburg, Germany, with “Two Drugs are Better Than One”. He first presented data on so-called clinical inertia, bemoaning the number of years it takes for patients under suboptimal glycemic control to have their therapy intensified. This is in spite of prevailing treatment guidelines suggesting intensification if targets are not achieved at 3 months. Dr. Seufert emphasized that the traditional ‘treat-to-failure’ approach (Figure 6) does not serve patients well: a single agent prescribed, waiting
for the HbA1c to rise before a second drug is added, etc. Such a strategy exposes patients to a legacy of poor control, with the potential for irreversible vascular complications to become established. He then reviewed the pathogenesis of diabetes—a multifactorial disease with biological defects emanating from multiple organ systems, including muscle, liver, fat, pancreas, kidney, gut, and brain. Most of these can be addressed pharmacologically, but multiple treatments are usually necessary.

Prof. Seufert proposed that patients will do better with early combined therapy, targeting more than one of the defects simultaneously. He presented observational data indicating a higher prevalence of CV complications of between 20-26% in patients whose anti-hyperglycemic regimen is not advanced when needed (Kaul SA et al., Cardiovasc Diabetol 2015;14:100). The reasons for clinical inertia were next explored—both patient and clinician factors. From the patient’s standpoint, there may be a lack of understanding of the impact of poor glycemic control, the fear of hypoglycemia, and/or difficulty in maintaining adherence to therapies. From the clinician’s standpoint, there may be reluctance to intensify therapy in asymptomatic patients, a lack of appropriate infrastructure to address lifestyle habits, and also possible lack of familiarity with or confidence in newer agents.

Several studies confirming the short-term glycemic benefits of two drug combinations vs. monotherapy were reviewed, most including combinations of DPP-4 inhibitors and SGLT-2 inhibitors with metformin. Newer data with novel fixed formulations of GLP-1 receptor agonists plus basal insulins were mentioned as well.

In summary, in spite of prevailing clinical guidelines that encourage either combination therapy in certain individuals from the outset or aggressive sequential add-on approaches, clinical inertia prevails. The answer, according to Dr. Seufert, is combination therapy—ideally as early in the course of disease as possible.

The next speaker, Prof. Stefano Del Prato from the University of Pisa, Italy addressed a similar topic: “From the Start: Combination Therapy.” Dr. Del Prato echoed many of the points made by Dr. Seufert. He described the worrisome growing global prevalence of diabetes and the tens of millions of people throughout the world who are predicted to develop its myriad of complications over the next 30-40 years. This will have disastrous consequences for health care systems in many countries. He reminded the audience of the highly complex pathogenesis of Type 2 diabetes, expanding upon the points made earlier in the morning. Prof. Del Prato feels that the only logical approach to therapy is to address two or even three of the pathophysiological defects of the disease simultaneously and ideally at the time of initial diagnosis. He reviewed recent data from the University of Texas/San Antonio group showing that the somewhat controversial approach of initial triple therapy with metformin, pioglitazone, and a GLP-1 receptor agonist achieved better and more sustained HbA1c control and with less hypoglycemia over sulfonlureas combined with insulin.

Dr. Del Prato mentioned the ongoing GRADE trial in the US and the VERIFY trial in Europe that could help provide insights into the optimal combination therapy beyond metformin. Unfortunately, results will not be available for several years. Until then, he encouraged the audience to consider combination therapy from the start to tackle the pathophysiological complexity of the disease, taking advantage of complementary mechanisms of action, while also providing a balance between efficacy and side effects so as to optimally individualize care. Such an approach is apt to result in more sustained efficacy and a likely reduction in long-term complications.

In the Q&A session that followed, audience members remarked about the lack of any clinical trial data to demonstrate that early initial combinations have any measurable clinical benefit other than quicker HbA1c reduction over traditional sequential therapy. So, is combination therapy at diagnosis really worth the additional costs? Of course, in the real world, treatment guidelines are not followed consistently. Therefore, the early combination therapy approach may be a useful strategy if simply to address some of the logistical issues in many practices that tolerate or even encourage clinical inertia.

The concluding presentation of the symposium was by Dr. John Wilding from the University of Liverpool, UK, entitled, “Clinical Profiling As a Key to Optimal Drug Selection.” The speaker admitted that, at present, there is very little data to predict which drug will work best in which patient. As a default, clinical decisions are often based on the potential for adverse effects or formulary restrictions at a national level. In contrast, Dr. Wilding gave two examples of uncommon forms of diabetes that clearly respond best to a single drug. For instance, the type of Maturity Onset Diabetes of Youth (MODY) due to a mutation in the hepatic nuclear factor (HNF)-1a gene is a disease that is ideally treated with sulfonylurea monotherapy. Another example provided was Latent Autoimmune Diabetes of Adulthood (LADA), a more slowly progressive form of autoimmune diabetes, similar to Type 1 diabetes. This, of course, responds best to insulin. Beyond these, however, arriving at the perfect formula beyond metformin for an individual patient is often an exercise in trial and error.

Prof. Wilding defined ‘clinical profiling’ as the “smart selection of treatments based on patient characteristics to optimize outcomes.” Currently, however, the variability in glycemic responses to a specific drug from patient to patient can be quite alarming—few patients follow the mean HbA1c response reported from clinical trials. He looks forward to the day when data from pharmacogenetics may better inform our clinical decisions in this heterogeneous disease, so that we can eventually practice precision medicine. Until then, except for certain specific and usually rare types of diabetes, clinicians still need to resort to the “N of 1 trial.”

After the presentation, audience members commented that recent data from CV outcome trials suggest that using Hba1c as our sole treatment metric may be misguided—that certain individual patient characteristics, such as coronary artery disease, heart failure, or chronic kidney disease (CKD) may necessitate specific glucose-lowering therapies for their non-glycemic effects.
**Obesity: Diabetes’ Frequent Partner**

Obesity is common, serious, and costly. According to the CDC more than one-third of U.S. adults (34.9% or 78.6 million) were obese during surveys conducted from 2011-2014. Overweight/obesity is the single best predictor of Type 2 diabetes, with the majority (~90%) of such patients being overweight or obese. Treatment of obesity with bariatric surgery is associated with reduced risk of diabetes and incidence of microvascular complications, as was highlighted in presentations made during the week at the 2016 EASD annual meeting.

**Bariatric Surgery Update**

Taube et al. from Sweden and Finland reported on the importance of durable diabetes remission for the prevention of microvascular complications (abstract 73). Microvascular events (assessed as the first occurrence of either retinopathy, nephropathy, or neuropathy) were tracked in 343 patients with baseline Type 2 diabetes (mean age 48.7 ± 5.9 years, BMI 42.1 ± 4.7 kg/m²) treated by bariatric surgery (banding [n=61], vertical banded gastroplasty [n=227], and gastric bypass [n=55]). At a follow-up examination conducted 15 years after bariatric surgery, patients who were in remission (30% of the cohort) had an ~80% lower risk of microvascular events compared to those who remained diabetic (incidence of 8.0 and 26.0 per 1000 person-years, adjusted hazard ratio [HR] 0.19 [95% CI: 0.07, 0.50], p=0.001). These data, which essentially represent a “responders analysis”, with all of its inherent biases, are still important and demonstrate the benefits of diabetes remission after bariatric surgery on important clinical outcomes.

The same research group reported that bariatric surgery also reduces the long-term incidence of microvascular disease in obese patients with prediabetes, this time using a control group of individuals not receiving such procedures (abstract 1026). They tracked and compared the incidence of the microvascular complications noted above in 301 participants with baseline impaired fasting glucose treated by bariatric surgery to that of 290 under usual care. Over an impressive median follow-up of 19 years, bariatric surgery reduced the risk of microvascular events also by ~80% (incidence of 3.9 and 18.7 per 1000 person-years in the surgery and control groups, respectively; HR 0.19, p<0.001]). At the follow-up examination, more than 3-fold fewer patients treated with bariatric surgery progressed from prediabetes to diabetes (15.6% vs. 54.5% of the control group). Those with incident diabetes had a higher rate of microvascular events compared to those who had not developed diabetes (9.3 vs. 2.9 per 1000 person-years, respectively, p=0.009, in the surgery group and 22.6 vs. 14.0 per 1000 person-years, respectively, p=0.028, in the control group). Bariatric surgery reduced the risk of microvascular events in both those that developed diabetes (HR=0.36; p=0.007) and in those who did not (HR=0.20; p<0.001). This study is even more convincing than the prior, and its results should be considered in our discussions with obese patients with prediabetes.

Capocchia and Italian associates reported long-term results seven years following laparoscopic sleeve gastrectomy for 195 obese patients (43 male, mean age 43.9 ± 10.6 years, weight 123 ± 21 kg, BMI 44.6 ± 6.8 kg/m², 78 with Type 2 diabetes) (abstract 598). Sleeve gastrectomy led to a weight loss comparable to other bariatric procedures, with body weight and BMI nadir (79.2 ± 16.1 kg, BMI 28.6 ± 5.3 kg/m²) reached after two years. Afterwards, modest regain (22±6.7%) began in less than half of patients operated (52% of diabetics and 37% of non-diabetics) to levels far below preoperative weight. Type 2 diabetes resolved in more than half after surgery (56% and 60% of those without and with regain, respectively). Partial resolution (defined as FPG <110 mg/dL and HbA1c <6.5%) and complete resolution of Type 2 diabetes (FPG <100 mg/dL and HbA1c <6.0%) were observed in 72% (56/78) of patients. However, according to OGTT, only 40% had an absolutely normal post-challenge glycemic curves. Forty-six percent had either impaired glucose tolerance (2-hour glucose 140-199 mg/dL) or a blood glucose ≥200 mg/dL at ‘unofficial’ earlier time points during the OGTT. Fourteen percent had evidence of overt diabetes (i.e., 2-hour glucose ≥200 mg/dL).

**Mechanistic Insights**

Interested in the mechanism behind appetite reduction and weight loss following bariatric surgery, Svane and Danish associates conducted a randomized, placebo-controlled, cross-over study of 12 patients with normal glucose tolerance (mean age: 35.4 years, 8 female, mean BMI: 33.5 kg/m²) ~5 months after Roux-en-Y gastric bypass (RYGB) (abstract 74). They hypothesized that these post-surgical benefits result from exaggerated secretion of the appetite-inhibiting gut-hormones, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY).

On 4 separate study days, participants received: placebo; the GLP-1 receptor antagonist (GLP-RA), exendin 9-39; the dipeptidyl-peptidase 4 (DPP-4)-inhibitor sitagliptin (which, in addition to blocking degradation of GLP-1, also blocks conversion of secreted PYY1-36 to its active form, PYY3-36); and the combination of GLP-RA and DPP-4 inhibitor. On each study day, the participants received a standard mixed meal test (356 kcal, 53% of energy from carbohydrate, 33% from fat, and 14% from protein) followed 4 hours later by an ad libitum pasta with meat sauce meal (energy content 533kJ/100g, 53% carbohydrate, 33% fat, 14% protein). Data were analyzed by use of linear mixed effects models.

Combined administration of sitagliptin/ exendin 9-39 (i.e., combined blockade of actions from both GLP-1 and PYY) increased ad libitum food intake by ~20% in RYGB-operated patients. In contrast, neither GLP-1 receptor blockade alone nor DPP-4 mediated lowering of active PYY alone affected food intake. Exendin 9-39 markedly increased PYY3-36 concentrations compared with placebo (p < 0.01), whereas significantly decreased concentrations were seen during concurrent administration of sitagliptin/exendin 9-39 compared with exendin 9-39 alone (p < 0.01). Intact GLP-1 levels increased significantly with exendin 9-39 alone, with sitagliptin alone, and even more with the combination. The investigators concluded that the combined effects of GLP-1 and PYY3-36 play a major role in decreased appetite and weight loss after RYGB. They also suggested that enhancing the actions of these two gut-derived peptides simultaneously may be an effective future non-surgical treatment of obesity.

**Steatosis Stories**

Steatosis and steatohepatitis are extremely common in patients with Type 2 diabetes. The latter can progress to cirrhosis and liver failure, and
Cardiovascular complications remain the most lethal complication of diabetes. More insights in this relationship were provided this week in Munich.

**Diabetes and Recurrent Stroke**

Over 9% of recurrent strokes is attributed to diabetes mellitus, and 16% of diabetic patients over 65 years of age die following a stroke. Given the incidence and morbidity/mortality of stroke in this setting, Bourdakis and investigators from Greece conducted a study of 125 Type 2 diabetes patients (65 male, mean age 69 years, diabetes duration 15 years) and a history of first-ever ischemic, non-cardioembolic stroke to determine the influence of dysglycemia on risk of recurrent event (abstract 1153). Smokers (>3 pack-years) and patients with atrial fibrillation, coronary artery disease, or heart failure (NYHA >3) were excluded. Patients were followed every 6 months for at least 2 years, with BMI, HbA1c, total cholesterol, LDL-cholesterol, and triglycerides regularly tested and treated accordingly to local standard. Patients' anti-coagulant therapy remained stable.

**Figure 7. Change in Liver Fat**

![Figure 7. Change in Liver Fat](image)

Intrahepatic fat content significantly decreased after intermittent fasting (Type 2 diabetes: 9.9±2.6 to 7.9±2.7%; controls: 8.9±2.2 to 6.7±1.8%), but whole body insulin sensitivity, FPG, HbA1c, and overall percent body fat were actually unchanged.

Another study exploring the effect of diet on steatosis was presented by Luukkonen and researchers from Finland and the UK. They compared the effects of overfeeding different diets on liver fat content (abstract 18). Thirty-eight subjects (21 female, mean age 48 years, BMI 31 kg/m², liver fat 4.7% [normal <2%]) were randomized to an enriched diet (+1000 extra calories/day) from either unsaturated fat (n=12), saturated fat (n=14), or carbohydrates (n=12) for 3 weeks. Overfeeding of all 3 diets increased liver fat, the greatest change occurring with saturated fat (Figure 7). Composition of the diet affected the source of liver fat. The carbohydrate-enriched diet increased liver fat via hepatic de novo lipogenesis, the saturated fat-enriched diet by increased adipose tissue lipolysis, and the unsaturated fat-enriched diet by unsaturated fat in the liver (decreased adipose tissue lipolysis). The investigators concluded that although increased carbohydrate diet has been implicated in non-alcoholic fatty liver disease (NAFLD), intake of saturated fat may be more harmful on liver fat accumulation.

In Sweden and co-workers reported that a paleolithic diet for 12 weeks (lean meat, fish, seafood, eggs, vegetables, fruits, berries, and nuts) improved liver fat (~77%), peripheral insulin sensitivity (~57%), adipose tissue insulin sensitivity (~3.4%), and insulin clearance (~14%) in patients with Type 2 diabetes (abstract 17). We look forward to more evidence from bariatric and hepatology researchers on strategies to reduce total body and hepatic fat, in order to improve clinical outcomes in our obese patients.

**Figure 8. Ischemic Stroke Recurrence by HbA1c**

![Figure 8. Ischemic Stroke Recurrence by HbA1c](image)

After two years, 79% of men and 81% of women achieved LDL goal; 95% and 100%, respectively, achieved triglycerides goal; 40% and 32%, respectively, met target HbA1c, yet 23% and 20%, respectively, experienced an increase in BMI. At 2-year follow-up, 14.4% of the patients (15.3% of men and 13.3% of women) had already had a second cerebral event. Chronic hyperglycemia was found to be related to the risk of recurrent stroke (Figure 8). On the basis of these findings, the investigators suggested that HbA1c might be a satisfactory predictor of future stroke recurrence among diabetic patients. We found these essentially cross-sectional data unconvincing, since the vast majority of patients with diabetes has a HbA1c >6%. The investigators should have conducted multifactorial adjustments to determine whether HbA1c was an actual risk factor for recurrent stroke.

**Link to A-fib**

Using data from several national Swedish Registries, Karayiannides from the Karolinska Institute and co-workers identified 326,832 persons with a diagnosis of atrial fibrillation between 2006 and 2012, who survived for at least 30 days, and followed them for mortality and a composite of non-fatal CV events (first of
mortality, heart failure, ischemic stroke, or MI) until the end of 2013 (abstract 1154). Patients ≤20 years old and those with valvular atrial fibrillation were excluded.

Diabetes was present in 17.7% (n=57, 953). The most frequent events are shown in Figure 9. Patients with atrial fibrillation and diabetes had high event rates for mortality and heart failure, with levels far exceeding event rates for stroke.

After adjustments for comorbidities, medication, and socioeconomic factors, diabetes was a risk factor for mortality (HR 1.28 [95% CI 1.25, 1.31], combined non-fatal CV events (HR 1.22 [1.20-1.25]), and bleeding complications (HR 1.12 [1.06-1.19]).

The standardized mortality ratio compared to the general population for patients with atrial fibrillation and diabetes was 2.06 (95% CI: 2.00, 2.12). For patients with atrial fibrillation but without diabetes the HR was only 1.33 (95% CI: 1.31, 1.35). The investigators concluded that increased awareness of the link between diabetes and atrial fibrillation is needed.

**Mortality in Patients with Heart Failure**

Other researchers from Karolinska used data from the Swedish National Heart Failure Registry between 2003-2011, identifying patients with a reported HbA1c (n=2,181), and followed them for all-cause mortality until the end of 2014 (median follow-up period, 4.4 years) (abstract 1113). 921 patients did not carry a diabetes diagnosis (mean age 71±12 years, 66% men, 14% ejection fraction ≥50%) of whom 15% (n=136) had previously undetected diabetes (HbA1c ≥6.5%) and 30% (n=273) were at high risk for its development (HbA1c 6.0-6.4%). In these patients, long-term mortality increased directly with HbA1c (log-rank p<0.0001; Figure 10).

Among the 1,260 patients with previously established diabetes (mean age 72±11 years, 66% men, 18% ejection fraction ≥50%), however HbA1c did not predict mortality in this condition, (log-rank p=0.10). In the group without previously diagnosed diabetes, the adjusted hazard ratio for mortality with HbA1c ≥6.5% vs. <6% was 1.44 (95% CI: 1.11, 1.87). The corresponding hazard ratio for those with known diabetes was 0.97 (95% CI: 0.76, 1.25).

The investigators concluded that screening for dysglycemia in populations with heart failure is important and glucose control may need to be initiated early in the development of dysglycemia. While the results of this study are interesting, it may be premature to suggest that they imply earlier treatment will mitigate the mortality risk of heart failure in this population.

**News on the Treatment Front**

Acetylsalicylic acid (ASA) use is recommended for primary prevention of atherosclerotic cardiovascular disease (ASCVD) for people with and without diabetes when the ASCVD benefit outweighs the risk of gastrointestinal (GI) hemorrhage. Crain and associates from Minnesota evaluated the use of ASA in a primary care setting. Their cohort included 6,065 adults with diabetes (mean age 55.6 years, mean 10-year ASCVD risk 27.9%) and 10,165 adults meeting pre-specified criteria for high ASCVD risk without diabetes (mean age 58.4 years, mean 10-year ASCVD risk 24.6%). The investigators sought to determine concordance between ASA algorithm recommendations and documented use (abstract 72). The algorithms recommend ASA if ASCVD risk scores were high and consistent with benefit greater than GI bleeding risk using criteria from the US Preventative Services Task Force. ASA is not recommended if the ASCVD benefit was low or if major contraindications were identified (anticoagulant use or history of intracerebral hemorrhage).

For the targeted population with high CV risk, ASA was recommended for 3,842 (63.3%) patients with diabetes and 7,552 (74.3%) without diabetes. Among those with ASA recommended, it was underused in 761 (19.8%) with diabetes and 5,638 (74.4%) without diabetes. Among patients for whom ASA was not recommended, it was overused in 1,322 (59.5%) with diabetes and 883 (33.8%) without diabetes. The investigators recommended strategies to ensure greater evidence-based use of ASA, such as providing electronic clinical decision-making support, thereby helping providers more accurately assess individualized risks and benefits of ASA.

Sattar et al. presented 1-year results from the OSLER open-label extension (to 12-week randomized controlled) studies of the PCSK9 inhibitor, evolocumab, in hyperlipidemia patients.
with \( n=190 \) and without \( n=1612 \) Type 2 diabetes enrolled at European study sites (abstract 1106). Patients received standard of care, including statins, with or, without evolocumab, with results of both studies’ regimens (420 mg monthly or 140 mg every 2 weeks) combined for the latter in the analyses.

After one year, evolocumab as add-on therapy to statins led to significant reductions in lipid levels (Figure 11), notably in LDL-cholesterol and lipoprotein A, as compared with standard care alone, allowing Type 2 diabetes patients to reach LDL-cholesterol treatment goals.

Of course it remains unknown if this never injectable agent that is extremely expensive will actually reduce CV events.\(^*\) Those data should be reported over the next 1-2 years.

Given that cardiovascular disease remains the leading cause of death in our patients with diabetes, these and other studies are most welcome at our international diabetes meetings.

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**Take a Breath!**

Köpf and German investigators conducted a prospective observational study to investigate the impact of diabetes and dysglycemia on pulmonary function (abstract 1091). 164 participants (controls \( n=21 \); pre-diabetes \( n=43 \); diabetes \( n=100 \)) without established pulmonary disease (e.g., no asthma, COPD, pulmonary hypertension, etc.) underwent testing of pulmonary function, HbA1c, UACR, and measurement of advanced-glycation-end products under the skin (skin-AGE). According to one-way-ANOVA, there were significant differences in vital capacity (VC; \( p<0.01 \)), single breath diffusion capacity (DLCO; \( p<0.01 \)), and total lung capacity (TLC; \( p<0.05 \)) between healthy controls, pre-diabetics, and diabetic patients, with a continuous decrease of all parameters with progression to diabetes. Correlation analyses showed significant associations: between HbA1c and decreased TLC \( (r=-0.35; \ p<0.01) \) and impaired DLCO \( (r=-0.23; \ p<0.05) \); between increased UACR and decreased TLC \( (r=-0.55; \ p<0.001) \) and impaired DLCO \( (r=-0.40; \ p<0.01) \); and between increased skin-AGE and impaired DLCO \( (r=-0.29; \ p<0.05) \). This study suggests a new complication of long-standing diabetes, such as diabetes, may lead to a change in body composition, increase in insulin resistance, deterioration of metabolic control, promotion of dyslipidemia and heart disease, and increase in bone fragility. Furthermore, hypogonadism affects sexual behavior and performance and may decrease quality of life. In a single-center study, Martins et al., from Portugal measured gonadal function in 127 overweight male diabetic patients, 28% with Type 1 and 72% with Type 2 (mean age 60±15 years, BMI 28.4±4.8 kg/m\(^2\)), with long-standing disease (18±11 years) and fair metabolic control (HbA1c 7.9±1.5%) (abstract 1068). Microvascular disease was common (30-50%), as was hypertension (76%) and dyslipidemia (56%). Testosterone values ranged from 19 to 1467 ng/dL.

More than half of study participants (75, 59%) had hypogonadism (29 with testosterone <240 ng/dL; 46 with testosterone 240-359 ng/dL), which was almost always central in origin (i.e., hypogonadotropic, 92% with low or inappropriately normal LH/FSH) that was not significantly related to age. Total testosterone levels were significantly lower in those with peripheral neuropathy than in those without (290±100 vs. 384±206; \( p<0.05 \)), and were inversely related to obesity (BMI: \( r=-0.250; \ p<0.01 \)) and to some extent metabolic control (HbA1c: \( r=-0.153; \ p<0.1 \)). The investigators concluded that hypogonadism is common among men with diabetes, driven more so by their metabolic status than age.

One issue we’d raise is the validity of total testosterone level in obese men. We know that sex hormone binding globulin (SHBG) tends to be low with increasing BMI, body fat, and aging. Thus, any definitive study must employee free testosterone measurements as a safeguard against falsely low total testosterone levels related to altered binding protein concentrations. Nonetheless, we agree that hypogonadism is common in Type 2 diabetes and may need to be treated if symptoms are present and there are no contraindications for androgen replacement therapy.

**Complication Clustering in Type 1 Diabetes**

Bjerg from Denmark examined the pattern of co-occurrence of microvascular complications in a cohort of 2,391 Type 1 diabetes patients (1248 male, mean age 52±15 years, diabetes duration 27±14 years) (abstract 359). The prevalence of nephropathy, neuropathy and retinopathy was 37.3%, 38.6%, and 62.7%, respectively. The majority of patients (74.4%) had at least one microvascular complication, 29.1% had only one, 26.7% had two, and 18.4% had all three. Log-linear models showed 2-way interactions for all 3 complication pairs, but no evidence for 3-way interaction. Clustering occurred at both extremes of the 3-dimensional distribution of complications (Table 3), consistent with a strong shared etiology among the processes leading to each of the microvascular diseases. This is, of course, consistent with our current understanding of the etiopathogenesis of these complications.

**Table 3. Observed and Expected Prevalence of Microvascular Complications Among Patients With Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Observations ( n=2,391 )</th>
<th>Observed Prevalence (%)</th>
<th>Expected Prevalence (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>613</td>
<td>25.6</td>
<td>14.3</td>
<td>1.79</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>96</td>
<td>4.0</td>
<td>8.6</td>
<td>0.47</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>127</td>
<td>5.4</td>
<td>9.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>469</td>
<td>19.7</td>
<td>24.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Nephropathy + Neuropathy</td>
<td>57</td>
<td>2.4</td>
<td>5.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Nephropathy + Retinopathy</td>
<td>291</td>
<td>12.2</td>
<td>14.3</td>
<td>0.85</td>
</tr>
<tr>
<td>Neuropathy + Retinopathy</td>
<td>290</td>
<td>12.1</td>
<td>15.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Nephropathy + Neuropathy + Retinopathy</td>
<td>448</td>
<td>18.7</td>
<td>9.0</td>
<td>2.08</td>
</tr>
</tbody>
</table>

* The product is not labeled for the use under discussion or the product is still investigational.
After more than 3 decades of essentially negative trials, beneficial CV effects have now been documented for three separate glucose-lowering agents: the SGLT-2 inhibitor empagliflozin (EMPA-REG OUTCOME) and two GLP-1 receptor agonists, liraglutide (LEADER) and now semaglutide (SUSTAIN-6). News from these trials has given encouragement to clinicians and investigators: We can indeed improve CV outcomes in our patients with Type 2 diabetes with glucose-lowering drugs. However, it appears to have little to do with glucose-lowering itself, or the HbA1c target. Instead, it is likely the method with which we lower glucose that may hold the key.

This is, of course, a key question in clinical care. In fact, the FDA now mandates that any new diabetes medication that comes to market demonstrate at least CV safety in a large outcome trial. Prior to 2015, it had actually been very difficult to show that glucose lowering itself or the use of any specific agents improved CV outcomes (see Table 4).

The ‘big event’ from this year’s EASD meeting was the presentation of the SUSTAIN-6 trial’s results. This is the third GLP-1 agonist CV outcome trial to report, following quickly on the heels of LEADER with liraglutide, which was presented in June at the Scientific Sessions of the American Diabetes Association in New Orleans (see Diabetes 2016, volume 33, issue 3).

The GLP-1 agonists have been available now for about a decade but remain used in only a minority of patients with Type 2 diabetes—likely because they are injectables and also extremely expensive. Since their inception however, this category had been hoped to reap CV benefits for patients, because of their modest positive influence on several CV risk factors, in addition to glucose, such as weight, blood pressure, lipids, and inflammatory markers. When GLP-1 receptors were found in cardiac tissues and their activation was demonstrated to have anti-apoptotic effects, interest from the cardiology community grew further.

**LEADER Update**

In LEADER, a reprise of which was presented in Munich this week, 9340 patients were randomized to 1.8 mg of liraglutide or placebo by subcutaneous injections and followed for a median of 3.5 years. Fewer patients randomized to liraglutide experienced the primary outcome of 3-point MACE composite (CV mortality, non-fatal MI, and non-fatal stroke) (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=0.011 for superiority). As far as the individual components of the primary composite were concerned, CV mortality occurred in fewer patients on liraglutide than placebo (HR 0.78 [0.66, 0.93], p=0.007). This effect extended to a statistically significant benefit on all-cause death (HR 0.85 [0.74, 0.97], p=0.017). Non-fatal

**Table 4. Glucose-Lowering Therapies & CV Events: Clinical Trials**

<table>
<thead>
<tr>
<th>Class</th>
<th>UKPDS:</th>
<th>ORIGIN:</th>
<th>BARI-2D:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Metformin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>PROactive:</td>
<td>RECORD:</td>
<td>↔</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>SAVOR:</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>ELIXA:</td>
<td>LEADER:</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT2-inhibitors</td>
<td>EMPA-REG:</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

↑ = more CV events, ↓ = less CV events, ↔ = neutral effects
Following pieces of new data:

Pancreatic cancer events in the liraglutide group, but from last year’s meeting, the LEADER data hinted (see below).

Acute gallstone disease occurred more frequently in the liraglutide group (145 vs. 90 events, p<0.001), driven mainly by more acute cholecystitis.

There were less adjudicated pancreatitis episodes (19 in 18 liraglutide patients vs. 33 in 25 placebo patients). A larger number of pancreatitis cases were submitted to adjudication in the liraglutide group, but these did not qualify for documented episodes by prespecified criteria, mainly due to elevation of lipase alone (a common feature with GLP-1 agonist therapy). Interestingly, the presence of an elevated lipase during the trial occurred more frequently in liraglutide patients who did not develop pancreatitis. The data were actually statistically significant at the >3 times the upper limit of normal threshold. That is, liraglutide patients who developed this level of increased lipase were significantly less likely to be diagnosed with pancreatitis during the trial—in fact no one in the more than 200 patients who developed this level of liraglutide-induced lipase elevation developed pancreatitis.

Finally, further data were provided about the pancreatic cancer events. Overall, there were 13 adjudicated in the liraglutide group but only 5 in the placebo group. Four non-adjudicated pancreatic cancer events were subsequently found in patients who died prior to diagnosis. When those patients were added to the cases, the imbalance was less concerning at 13 vs. 9. Overall, all neoplasms were equal in number. Melanoma was also numerically more frequent in the liraglutide group, whereas prostate cancer and leukemia occurred more commonly in the placebo group. These numbers are all apt to represent chance findings.

**SUSTAIN-6 Results**

So, what about SUSTAIN-6? The ‘top-line’ results from the study were announced a few months ago – that the weekly injectable GLP-1 agonist semaglutide* also reduced 3-point MACE in this trial, which was substantially smaller than LEADER. On Friday morning, before a capacity crowd in the Minkowski Ballroom at the Munich Messe, Dr. Lawrence Leiter from the University of Toronto provided the background information on the trial. The design was similar to LEADER: 3297 patients with Type 2 diabetes and established CV disease or CV risk factors were randomized to one of two doses of semaglutide (0.5 or 1.0 mg) or matching placebo and followed for about 2 years. In all, more than 98% of patients completed the trial with vital status information available on more than 99%—excellent quality metrics for a modern clinical trial.

The mean age of the participants was 64.6 years, with a diabetes duration of nearly 14 years on average; about 61% were male. At baseline, the mean BMI was 32.8 kg/m² and HbA1c 8.7%. The mean eGFR was approximately 71 mL/min/1.73 m², with almost 28% having an eGFR <60 (i.e., CKD 3+). From a CV standpoint, as was the case with LEADER, about 83% had established CV complications with the balance (17%) having ‘subclinical CV disease’ owing, by inclusion criteria, to age of at least 60 years plus other risk factors. Sixty-one percent had overt ischemic heart disease, 33% with MI, 12% with previous stroke, and 24% with prior heart failure. Finally, evidence-based CV therapies were in widespread use (another quality measure of modern CV outcome trials): 96% on antihypertensive therapies (55% on ACE inhibitors and 40% on angiotensin receptor blockers), 81% on statins, and 81% on anti-thrombotic agents including aspirin. Regarding glycemic management, about 73% were using metformin, 42% on sulfonylureas, and 58% on some form of insulin.

**Figure 12. Primary MACE Outcome in SUSTAIN-6 (Kaplan-Meier Curve)**

![Kaplan-Meier Curve](image-url)
Next, Dr. Stephen Marso, of the University of Texas, Southwestern in Dallas, who also presented the primary findings from LEADER in June, presented the main SUSTAIN-6 results. The primary endpoint (also the usual composite of CV death, non-fatal MI, and non-fatal stroke) occurred in 108 (6.6%) of those randomized to semaglutide and 146 (8.9%) of those randomized to placebo (HR 0.74 [0.58, 0.95], p<0.001 for non-inferiority) for an absolute risk reduction (ARR) of 2.3% (Figure 12). In contrast to EMPA-REG, the lower dose (HR 0.77) appeared to have a somewhat intermediate effect between placebo and the higher dose (HR 0.71). (With empagliflozin, the event curves for both 10 and 25 mg doses were virtually superimposable for all pertinent outcomes.)

In contrast to the LEADER results however, there appeared to be no effect on CV mortality: 37 (2.2%) vs. 40 (2.4%) (HR 0.98 [0.65, 1.48]), possibly related to a shorter duration trial. Instead, the major effects with semaglutide appeared to be on both non-fatal MI (46 [2.8%]) vs. 64 [4.9%]; HR 0.74 [0.51, 1.08], p=0.12, ARR 2.1% ) and stroke (25 [1.5%] vs. 42 [2.5%]; HR 0.61 [0.38, 0.99], p=0.04). The RRR for stroke appears quite impressive, but the ARR was only 1.0%, due to small numbers of events. There was no effect on heart failure hospitalization (HR =1.11 [0.77, 1.61]).

A variety of sensitivity analyses were consistent with the primary outcome analysis, and there was little heterogeneity for the primary outcome between various prespecified subgroups including age, race, sex, baseline HbA1c, and renal function. There were a few interesting subgroup trends, however. First, the point estimate for the primary outcome was >1.0 in those with heart failure at baseline (HR=1.03 [0.64, 1.66]). There was a similar finding in the subgroup using insulin at baseline (HR=1.02 [0.64, 1.62]). Finally, the drug appeared to have a neutral effect in the 17% of the cohort who were included in the trial on the basis of age >60 and CV risk factors as opposed to overt CV disease (HR=1.00 [0.41, 2.46]). Such a ‘primary prevention’ cohort also appeared to experience no benefit from liraglutide in LEADER (HR 1.16=[0.83, 1.61]).

While there was no statistical heterogeneity for a difference in these subgroups (i.e., no interaction for either baseline heart failure, insulin use, or absence of CV disease), these trends raise some concern that in practice, the drug would be expected to result in a CV benefit only in those without heart failure, on oral agents, and with prevalent CV disease. A larger study would of course be needed to test the validity of that conclusion.

As for other outcomes, the drug appeared to reduce microvascular events, driven exclusively by improved new or worsening nephropathy (HR 0.64 [0.46, 0.88]). This composite was, in turn, driven essentially by less persistent macroalbuminuria. As with LEADER, there was a similar risk of more retinopathy (3.0% vs. 1.8%; HR 1.76 [1.11, 2.78], p=0.02). The reason for this finding remains unknown. As for safety, semaglutide was reasonably well tolerated, with the expected increase in GI side effects. No increase in either pancreatitis or in pancreatic malignancy was found.

One additional point we’d like to make: Despite the protocol’s mandate to maintain glycemic control to local standards in all patients, the HbA1c difference at week 104 of the study was -1.09% in the low-dose semaglutide group and -1.41% in the high-dose group. These differences were larger than that seen in LEADER, likely related to a more powerful agonist. These differences, however, call into question whether some of the results of the trial may relate to differences in glucose control. Ideally, because all patients were managed according to the usual standards of care, the differences in mean HbA1c between active therapy and placebo groups should be small, typically 0.3-0.4% or less. In LEADER it was 0.4% by 36 months and in SUSTAIN-6, as noted, it was well over 1% in the high-dose group. While no one any longer thinks that glycemic differences of this degree should affect CV outcomes, it might contribute to some of the renal outcomes. It might also explain the retinopathy findings, since rapid control of blood glucose has been reported previously to aggravate retinal ischemia in the early phases of some trials (e.g. the DCCT).

So, with SUSTAIN-6, the CV benefits of GLP-1 agonists are becoming clear. The initial trial of this type in this class, ELIXA testing lixisenatide (not yet available in the US) in post-acute coronary syndrome patients proved negative. However, LEADER and now SUSTAIN-6 makes it more likely that the class has CV benefits, although it may certainly vary from drug to drug.

### EMPA-REG Update

Earlier this week, we reported on the SGLT-2 inhibitors and reviewed the findings from the EMPA-REG OUTCOME trial, whose primary results were initially reported at last year’s EASD meeting in Stockholm, Sweden (see Diabetes 2016, vol. 32, issue 4 and Diabetes 2015, vol. 33 issue 3). Since that presentation, data from which were simultaneously published (Zinman et al. N Engl J Med 2015;373(22):2117-28), two follow-up papers have been released by the investigators, disclosing important benefits related to heart failure (Fitchett et al. Eur Heart J 2016;37:1526-34) and diabetic kidney disease (Wanner et al. N Engl J Med 2016;375:323-34). These results were presented in Munich this week in a symposium entitled: "EMPA-REG OUTCOME—One Year Later." The main new data are summarized below:

- The 38% reduction in CV mortality was contributed to by numerical reductions in each category: fatal MI, fatal stroke, fatal heart failure, sudden death, and “other CV deaths.” As a percentage, the categories contributing the most were sudden death, heart failure, and “other”, this latter category probably representing mostly unwitnessed sudden deaths.
- Reductions in heart failure hospitalizations were statistically similar in those with (HR 0.75 [0.48, 1.19]) versus without heart failure (HR 0.59 [0.43, 0.82]).

### Table 5. Primary Outcome Results and Components from 3 Recent Large Diabetes CV Outcome Trials

<table>
<thead>
<tr>
<th>EMPA-REG OUTCOME</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with event/analyzed</strong></td>
<td><strong>Patients with event/analyzed</strong></td>
<td><strong>Patients with event/analyzed</strong></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Empagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td>3 point MACE</td>
<td>0.86 (0.74-0.99)*</td>
<td>490/4687</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49-0.77)</td>
<td>172/4687</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>213/4687</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.24 (0.92-1.67)</td>
<td>150/4687</td>
</tr>
</tbody>
</table>
Reductions in CV mortality were also experienced by both those with (HR 0.67 [0.47, 0.97]) and without heart failure (HR 0.63 [0.48, 0.84]) either at baseline or during the trial. A composite outcome representing progression of renal disease (similar to the composite used in the LEADER trial above) was reduced 39% by empagliflozin (HR 0.61 [0.53, 0.70]). In contrast to the LEADER findings, most components of the composite contributed to this finding, including the development of new macroalbuminuria (HR 0.62 [0.54, 0.72]), doubling of serum creatinine (HR 0.56 [0.39, 0.79]), and initiation of renal replacement therapy (HR 0.45 [0.21, 0.97]).

To summarize, over the past year, three major diabetes CV outcome trials have had positive findings (See Table 5 for summary of findings). In addition, the Insulin Resistance after Stroke (IRIS) trial recently showed that the thiazolidinedione, pioglitazone, reduced MI and stroke risk by 24% in nearly 3,500 patients with prior stroke who had insulin resistance (but not diabetes). So, we may be entering a new era in diabetes care. We finally have data to support the contention that the manner in which glucose levels are lowered is likely to be more important for CV outcomes than glucose lowering itself. Moreover, we suspect the findings of these trials will become incorporated into treatment guidelines at some point in the near future.

Hypoglycemia is a common and well known adverse effect of several classes of medications used to manage diabetes. Cardiovascular outcomes associated with hypoglycemia are not as well described and/or studied. Heller et al. from the UK, presented data from the previously published EXAMINE trial (N Engl J Med 2013; 369(4):1327-35), further analyzing hypoglycemia and its relationship to CV events (abstract 83). The trial was designed to evaluate rates of MACE among Type 2 patients with recent acute coronary syndrome who were randomized to the DPP-4 inhibitor, alogliptin, or placebo, added to their background glucose-lowering therapy. The main result was neutral—alogliptin neither decreased nor increased MACE. During the trial, 354 patients experienced hypoglycemia, with no differences between groups: 6.7% and 6.5% on alogliptin and placebo, respectively. Rates of serious hypoglycemia were low and also comparable (0.7% on alogliptin and 0.6% on placebo). Hypoglycemia was not defined numerically, rather was captured and assessed by study investigators in the initial trial. Severe hypoglycemia was defined as events serious enough to require hospitalization or considered life-threatening. In this investigation, a Cox proportional hazards model adjusted for baseline covariates (age, gender, HbA1c, diabetes medications) to assess the relationship between MACE and hypoglycemia. Consistent with other trials, there was a significant increase in MACE in patients who developed serious hypoglycemia (12/34, 35.3%) when compared to those who did not (609/5346, 11.4%) (adjusted HR: 2.42 [95% Cl: 1.27, 4.60]; p=0.007). There was also a statistically significant increase in MACE in those who experienced any hypoglycemia (64/354, 18.1%) versus those without any hypoglycemia reported (557/5026, 11.1%) (adjusted HR: 1.38 [1.05, 1.80]; p=0.019). From this analysis, the investigators suggested that hypoglycemia may have additional negative outcomes beyond impairment of cerebral function and that the association between hypoglycemia and cardiac events should be considered when choosing therapy. Also, as pointed out during the Q&A portion of the presentation, the available data can only indicate association and not necessarily causality. That is, patients who are more vulnerable to ischemic events could simply be more vulnerable to hypoglycemia. Further study is obviously warranted.

As we all know, certain classes of medications used to manage diabetes are associated with higher rates of hypoglycemia than others. Holden et al. from Wales evaluated hospital admission rates for hypoglycemia based on glucose-lowering regimen and within each regimen, by HbA1c values (abstract 317). Data were retrospectively analyzed from the UK Clinical Practice Research Datalink linked to Hospital Episode Statistics (HES) from patients with Type 2 diabetes and treated with one of six medication groups for more than 90 days. The groups consisted of: (1) insulin monotherapy (n=4,107); (2) sulfonylurea monotherapy (n=8,738); (3) a composite of regimens with known hypoglycemia risk (including insulins, sulfonylureas, or meglitindes as monotherapy or in combination with metformin) (n=39,361); (4) a composite of regimens with higher hypoglycemia risk, but excluding insulin (sulfonylureas or meglitindes as monotherapy or in combination with metformin) (n=30,036); (5) metformin monotherapy (n=46,064); and (6) a composite of low-risk regimens (metformin monotherapy or acarbose, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, and thiazolidinediones as monotherapy or in combination with metformin) (n=60,131). HbA1c values were categorized as lower (< 7%), moderate (7% to ≤ 8.5%), high (8.5% to < 9.5%), and very high (> 9.5%). Over a 10-year period (2004-2013), a total of 1,195 hospital admissions relating to hypoglycemia were identified. As might be expected, insulin monotherapy was associated with the highest rate of hypoglycemia per 1000 person-years (Figure 13).

With respect to categories of HbA1c values, insulin exposure was associated with increased admission rates in the majority of categories, with the exception HbA1c values in the ‘moderate’ range. In patients receiving any secretagogue, a lower HbA1c was associated with increased risk for hospital admission. Although admission rates varied by regimen and level of glycemic control, drug classes known for hypoglycemia risk (e.g., insulins, sulfonylureas) contributed to the vast majority of hospitalizations.
Insulin-related hypoglycemia was investigated from a “self-reported” perspective by Jain and multinational colleagues (abstract 823). Patients with Type 1 (n=1,016) or Type 2 (n=6,273) diabetes in Bangladesh, Colombia, Egypt, Indonesia, the Philippines, Singapore, South Africa, Turkey, and the UAE were distributed a self-assessment questionnaire. The non-interventional International Operations Hypoglycemia Assessment Tool (IoHAT) study analyzed patient diaries completed at baseline and after a 28-day prospective reporting period, as well as a 6-month retrospective review of hypoglycemia awareness and recall of severe events in the previous 4 weeks. Approximately 90% of patients completed the 28-day diary. The majority of patients reported hypoglycemic events in the prospective period (97.4% for Type 1 and 95.3% for Type 2 diabetes), with significantly lower rates (p<0.001) of recall in the retrospective time period (Type 1: 72.7%, Type 2: 48.1%). However, nocturnal hypoglycemia was reported at a significantly lower rate (p<0.001) in the prospective versus retrospective group. Close to one-half (48%) of patients with Type 1 diabetes and 12.6% of those with Type 2 reported at least one case of confirmed hypoglycemia (capillary blood glucose <56 mg/dL) in the prospective patient diaries. The investigators concluded that this is the first patient-reported dataset from the participating countries and that hypoglycemia is likely under-reported and under-estimated.

Lastly, Hambling et al. from the UK assessed hypoglycemia resulting from apparent overtreatment in the elderly, particularly in those with CKD (abstract 827). The investigators reminded their poster viewers that the elderly are particularly vulnerable to adverse consequences of hypoglycemia given their advanced age, diabetes duration, multiple comorbidities and polypharmacy (see page 7). They reviewed that CKD, as a co-morbid condition, is the most common cause of drug-induced hypoglycemia, especially in patients receiving insulin and/or sulfonylureas. Both the International Diabetes Federation and the International Society of Nephrology accordingly advise a cautious approach to glycemic targets (avoid HbA1c <7%), advocating for patient safety ahead of strict control. This is consistent with the current ADA-EASD guidelines. A cross-sectional, observational study was conducted in elderly patients (≥70 years old) with Type 2 diabetes, with and without CKD, assessing glycemic management and prevalence of ‘overtreatment’ with sulfonylurea and/or insulin. A primary care population from 16 general practices in the UK was used as the data set.

A total of 3,863 (15.7%) of the 24,661 patients ≥70 identified had a diagnostic code for diabetes. Over one-third (35.7%) had received a prescription for an insulin and/or sulfonylurea over the previous 90 days (824 [59.8%] for sulfonylureas; 410 [29.1%] for insulin; and 154 [11.2%] for both). Among those with Type 2 diabetes, and patients receiving insulin and/or sulfonylureas, 644 (47.8%) had documented CKD with an eGFR <60 mL/minute (25.5% with CKD 3A; 17.1% with CKD 3B; 5.2% CKD 4 or 5). Those with CKD tended to be older than their non-CKD counterparts (80 years [IQR 75-84] vs. 76 years [IQR 72-81]), with no significant difference in average HbA1c (7.5%). The percentage of patients prescribed sulfonylureas declined with worsening of CKD; however, the percentage of patients prescribed insulin and/or combination insulin and sulfonylureas demonstrated a significant increase (p<0.001) with diminishing kidney function. Investigator-defined ‘overtreatment’ was prevalent, but similar between groups (with/without CKD). The proportion of patients achieving an HbA1c <7.0% was 30.3% with CKD and 29.5% without, and the proportion of those attaining an HbA1c <6.5% with and without CKD was 13.3% and 10.9%, respectively (p=0.351).

Although hypoglycemic events were not documented, the investigators concluded that more than half of the patients in this elderly cohort had evidence of CKD and were prescribed sulfonylureas and/or insulin, placing them at risk for hypoglycemia.

Additionally, more than one-third was potentially overtreated based on attainment of aggressive HbA1c targets, mandating quality assurance programs for safer care.

We have some discomfort with studies that assign categorization of overly aggressive therapy when the individual details of specific cases are not available. For example, although insulin therapy with low HbA1c may be considered ‘overtreatment’ by the investigators, in the real world, a patient may be doing quite well at that level and without hypoglycemia. So, while studies like this can raise some reasonable concerns, they cannot be considered definitive. Nonetheless, we agree that hypoglycemia remains a significant consideration when managing patients with diabetes and that treatment targets should be relaxed in older, infirm patients, especially those with kidney disease.

The technology of CGM continues to evolve. Several studies were presented at the 2016 EASD annual meeting, describing improvements in implantable devices, glucose sensors, and even so-called ‘closed loop’ systems (CGM with insulin pumps).

Kropp and colleagues reported results from a 180-day, prospective, multicenter trial assessing the accuracy and longevity of the Eversense® CGM system, a new long-term implantable device (abstract 187). Eversense is a fluorescence-based glucose sensor and wearable transmitter allowing on-body vibration alerts that wirelessly communicate glucose results via smartphone. Patients with both Type 1 and Type 2 diabetes (n=71) from 7 clinical sites enrolled in the single-arm study for at-home and in-clinic use. Venous reference glucose measurements were taken during 8 in-clinic visits. The mean absolute relative difference (MARD) at 90 days over a fully glycemic range (40-400 mg/dL) between venous and CGM measurements was 11.6% (n = 21,527, SD 11.2% [95% CI: 10.9, 12.2%]). The MARD for reference glucose >75 mg/dL was 11.1% (n = 20,470; SD 10.1% [10.5, 11.7%]). The mean absolute difference (MAD) for reference glucose ≥75 mg/dL was 14.2 mg/dL (n = 1057; SD 13.5 mg/dL [12.1, 15.4 mg/dL]).

Sensor survivability was 82% at 90 days and 40% at 180 days, as determined by Kaplan-Meier analysis (median survival: 149 days, IQR 97-180 days). For those continuing beyond 90 days in the study, change in baseline HbA1c to last visit decreased from 7.5% to 7.2% (n=55, p<0.001). This degree of accuracy is similar to currently approved CGM devices, which are inserted by the patient subcutaneously approximately every 3-7 days.

A hybrid closed-loop system using the Medtronic MiniMed 670G pump was evaluated to establish safety for use in adolescents and adults (age 14-75 years) with Type 1 diabetes. Bergenstal et al. presented the results of a 3-month trial involving 124 patients (abstract 188). Baseline parameters were established after a 2-week run-in phase and compared with sensor glucose values at various study phases. Glycemic variability was calculated by the standard deviation (SD) and coefficient of variance of sensor glucose values. Each improved from baseline to study end: SD (56.5 mg/dL to 52.5 mg/dL, p<0.001) and coefficient of variance (37.6% to 34.7%, p<0.001).
Overall, mean HbA1c values changed by 0.5% (7.4±0.9 to 6.9±0.6%) with the proportion of patients achieving HbA1c <7% improving from 33.1% to 55.3%. Percentage of patients within all categories of desirable glucose ranges (71-180 mg/dL, not <70 mg/dL, not < 50 mg/dL, not >180 mg/dL) were statistically significantly improved for both 24-hour period and nighttime (10 pm to 7am) from baseline to study close (all p <0.001). Patients with the highest baseline HbA1c values experienced the greatest reductions in HbA1c and glycemic variability. There were no reports of DKA or device-related adverse events during the trial (12,389 patient-days of use). The investigators concluded that this hybrid closed-loop system is safe and effective for home use during both the day and nighttime.

The bionic hormonal pancreas,* a continuous multi-day, automated glycemic control device using insulin and glucagon, was evaluated in the home-use setting by Russell and US colleagues (abstract 189). Efficacy and safety in comparison with conventional insulin pump therapy were assessed in adults with Type 1 diabetes living at home without restricted diet or exercise in a random-order, 11-day crossover study. Mean glucose levels analyzed by CGM during days 2-11 in participants completing both arms of the study were compared: conventional 162±29 versus bionic pancreas 141±10 mg/dL, p <0.0001. Patients in the bionic pancreas arm demonstrated less time with glucose <60 mg/dL when compared to conventional insulin pump therapy (0.6±0.6% versus 1.9±1.7%, p<0.0001). From these data, the researchers summarized that the bionicrmal bionic pancreas, in the home-use study setting, improved mean glucose levels and time in hypoglycemia range when compared with conventional insulin pump in patients performing normal activities of daily living.

It is extremely encouraging to see the major advances that have been made in just the past few years in this field. It is our hope that fully integrated units will be available for clinical use over the next several years. This will certainly represent a welcome evolution in insulin therapy for our Type 1 patients.

The GLP-1 agonists are completing their first decade of use. As experience with them grows, the news appears generally good, but there remain concerns about side effects and costs. As diabetes progresses and initial monotherapy fails, the next-step choice is often unclear. Bailey and co-investigators compared the efficacy and safety of switching from sitagliptin to liraglutide in patients with Type 2 diabetes who were not controlled on combination sitagliptin and metformin therapy (abstract 1). Patients (mean age of 56 years, BMI 32 kg/m², HbA1c 8.3%) were randomly allocated to either liraglutide (n=202) or continuing sitagliptin (n=204) in a double-blind, double-drug trial in which each patient received both an injection and a tablet. HbA1c reductions were greater in those who switched to liraglutide than those remaining on sitagliptin (-1.14 vs. -0.54%, p<0.0001), and a greater amount of weight was lost with liraglutide (-3.31 vs. -1.64 kg, p=0.0001). Target goal of HbA1c <7.0% was reached in 50.6% of the GLP-1 agonist versus 26.9% of the DPP-4 inhibitor patients (p=0.0001), and HbA1c <5.5% in 29.5% and 9.9%, respectively (p <0.0001). This study demonstrates that liraglutide is potentially efficacious in combination with metformin in patients not reaching target with a DPP-4 inhibitor and metformin.

Dr. Philis-Tsimikas from Scripps Whittier Diabetes Institute, La Jolla presented 7-year efficacy and tolerability of once weekly exenatide in people with Type 2 diabetes (abstract 6). In the longest-running extension trial of a GLP-1 agonist, 122 (41%) of the original 295 participants in DURATION-1 completed treatment, showing that glycemic control and weight loss remained improved from baseline and adverse effects were minimal. By the 7th year of treatment, this cohort of baseline mean age 56 years had a mean HbA1c of 7.1±0.1 (-1.53% from baseline), weight of 97.1±1.6 kg (-3.9 kg from baseline), and 53% of the cohort did not require addition of new glucose-lowering medication. Importantly, no major hypoglycemic event was reported. Serious events included pancreatitis (n=2), pancreatic cancer (n=1), and acute renal failure (n=6), not necessarily related to therapy. We would caution that such open-label extension studies tend to overstate benefits, since non-responders tend not to persist their involvement.

Given the success of GLP-1 agonists in managing hyperglycemia and weight in people with Type 2 diabetes, Dr. Zinman and colleagues investigated its combined efficacy with insulin in people with Type 1 diabetes who had suboptimal glycemic control (HbA1c 7-10%) (abstract 2). (Currently, GLP-1 agonists are not approved for this indication.*) 1,398 patients (mean age 44 years, mean diabetes duration 21 years, mean HbA1c 8.2%, mean weight 86.2 kg) were randomized to receive one-daily injections of dulaglutide (1.8, 1.2, or 0.6 mg) or placebo as adjunct to insulin. HbA1c reductions of 0.34% to 0.54% were seen across the groups including placebo, indicating that liraglutide’s additional benefit was nominal and that closer monitoring may have been predominately responsible for the improved glycemia. Weight loss of -4.9, -3.6, and -2.2 kg occurred in liraglutide-treated patients, while weight increased in placebo users. Lisuraglutide at 1.8 mg and 1.2 mg resulted in statistically significant 8% and 5% reductions of total insulin dose, in comparison to increased insulin dosing for the placebo group. However, DKA occurred in 3, 1, and 4 people in the 1.8 mg, 1.2 mg, and 0.6 mg liraglutide groups, versus no events in the placebo group. This study indicates that the use of this GLP-1 agonist is limited in people with Type 1 diabetes, given modest benefits and an increased risk of ketoacidosis.

Using the AWARD clinical trial programs, Gallwitz and researchers from the US and Austria assessed the efficacy and safety of weekly dulaglutide by diabetes duration in a post-hoc analysis of several AWARD trials at six months (abstract 146). Patients were categorized by diabetes duration of <5, 5-10, and ≥10 years, evaluating HbA1c reductions from baseline. Pooled analyses of the five different trials demonstrated HbA1c reductions from baseline for all dulaglutide 1.5 mg and 0.75 mg, with the higher dose resulting in larger reductions. Dulaglutide appeared to reduce HbA1c equivalently in all three diabetes duration categories (1.2-1.3% with 1.5 mg and 0.9-1.0% with 0.75 mg). The impact on weight was similar regardless of dose and diabetes duration, ranging between 1 and 3 kg. Tolerability was generally good. The investigators suggested that this once-weekly GLP-1 agonist is an effective treatment option with efficacy independent of diabetes duration.

Several oral and poster presentations reviewed another long-acting, once-weekly GLP-1 receptor agonist, semaglutide,* which is not yet available in the US or Europe. One by Ahman and US and European researchers shared data on a phase 3, open-label comparative study of patients with Type 2 diabetes (n=813) randomized to receive semaglutide 1.0 mg or once-weekly exenatide ER 2.0 mg for 56 weeks (abstract 147). Primary endpoints included change in HbA1c and weight from baseline. The resultant HbA1c reduction for semaglutide and exenatide ER was -1.5% and
0.9%, respectively (estimated treatment difference [ETD]: -0.62%; p<0.0001). The proportion of patients achieving HbA1c <7% was 67% with semaglutide versus 40% with exenatide ER. Change in body weight from baseline was 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD: -3.73 kg; p<0.0001). Overall adverse events were similar between groups; however, semaglutide was associated with a higher incidence of GI-related effects (42% versus 33%), whereas injection site reactions were more common with exenatide ER (22% compared with 1%). (See page 16 in this edition for an update on the semaglutide CV outcome trial, SUSTAIN-6).

Lastly, the most recently approved GLP-1 receptor agonist in the US, the short-acting lixisenatide, was evaluated as a fixed-ratio combination product with insulin glargine (LixiLan) in comparison with each component alone. Guerci and European and North American colleagues conducted an open-label trial in Type 2 diabetes patients (n=1170) inadequately controlled (HbA1c 8.1%) on metformin with or without a second oral agent (abstract 804). Patients were randomized to receive the combination (n=469) or insulin glargine (n=467) or lixisenatide (n=234) for 30 weeks. At the close of study, mean HbA1c values were 6.5% for the combination, 6.8% for insulin glargine, and 7.3% for lixisenatide. Corresponding LS mean changes from baseline were -1.63%, -1.34% and -0.85%, achieving statistical significance for the combination compared with either component (p<0.0001). HbA1c comparisons consistently favored the combination of lixisenatide/glargine when analyzed by subpopulations of HbA1c (< or ≥8%); diabetes duration (<7 or ≥7 years), and body weight (<30 or ≥30 kg/m²). Additionally, there was no increase in hypoglycemia with the combination despite better glycemic control.

It remains to be seen to what degree, if any, the recent CV outcome trials with this class will affect their popularity.

The majority of people with Type 2 diabetes in the Western world are over the age of 65 years. Despite this fact, specific management strategies for elderly people are rarely discussed. In a well-attended symposium, an expert panel discussed key points in managing diabetes in the elderly. Specifically, higher prevalences of hypoglycemia, renal impairment, and frailty in these individuals require vigilance in screening, as well as modifications of glycemic targets and medication choices.

Dr. Brian Frier of the United Kingdom began the session by emphasizing that hypoglycemia is one of the most concerning and underestimated adverse events in older patients with diabetes. They are particularly at risk for hypoglycemia because the response to low blood glucose is blunted with aging. Also, other medications for comorbid conditions, such as beta blockers, will alter the thresholds for symptoms and counterregulatory hormone secretion. Adverse consequences of a hypoglycemia episode are also more likely to occur in elderly, including falls, fractures, and cognitive dysfunction. It is now established that older individuals who have hypoglycemic episodes are at greater risk of dementia (Feinkohl et al., Diabetes Care 2014;37:507). Also, this relationship is bi-directional in that elderly with cognitive impairment are also more likely to experience hypoglycemia (Punthakee et al., Diabetes Care 2012;35:787-93). For elderly with CV co-morbidities, the consequences of hypoglycemia may be even more precarious.

Dr. Guntram Schernthaner from Austria discussed the importance of individualized risk assessment in choosing glycemic targets and glucose-lowering therapies in the elderly. The elderly are more likely to have one or more co-morbidities than younger people with diabetes; in particular, one third have reduced GFR in the 30-59 range.

Glycemic targets need specific attention since overtreatment in the aged is common. For example in one survey, half of individuals over age 75 years receiving insulin or sulfonylureas had an HbA1c <7%, 29% had HbA1c <6.5%, and 11% had an HbA1c <6%, regardless of the presence of dementia (Tseng JAMA Intern Med. 2014;174:259-68). Several guidelines for diabetes management in elderly are available including the European Diabetes Working Party of Older Patients (EDWROP; Sinclair et al., J Am Med Dir Assoc 2012;13:497-502) and from the American Diabetes Association in the US (Kirkman et al. Diabetes Care 2012;35:2650-64). In general, the consensus is to advocate for a HbA1c of 7 to 8%, given data showing the best survival rates for elderly people with diabetes occurred when HbA1c was 7.5%, with a “U” shaped curve indicating worse survival for glycemic control greater or less than this threshold (Currie et al. Lancet 2010;375:481-9).

Recent trials of diabetes therapies have included a significant portion of people over age 65, so better data now exist to make treatment recommendations of certain medications over others. In general, according to Prof. Schernthaner, insulin and sulfonylureas are to be avoided given the importance of reducing hypoglycemia. For metformin, a recent safety review found that elderly with CKD stage 3 had benefit by being on this agent, while it wasn’t until stage 5 that mortality increased (Schernthaner et al. Nature Reviews Endocrinology 2015;11:697-9). However, it is noted from another, smaller study that metformin use was associated with an increased predicted risk of acute dialectsis, when compared with sulfonylureas (Carlson Diab Obes Metab 2016 online). This increased risk was primarily seen in women over age 60 and with eGFR <60. Dr. Schernthaner hypothesized that vulnerability to dehydration is the common link to potential adverse renal events when metformin is used. However, metformin has no known intrinsic negative renal effects. Indeed, precautions for metformin in CKD patients (recently relaxed in the US to allow its use so long as eGFR is >30) are related to the risk of lactic acidosis due to metformin accumulation.

DPP-4 inhibitors may be the safest medication to use in frail, elderly people and are generally well tolerated. The SGLT-2 inhibitors, especially empagliflozin, were recently shown to reduce all-cause mortality in an older diabetic population with multiple co-morbidities (see page 16). Liraglutide has also been recently shown to reduce all-cause mortality, and is a convenient alternative to prandial insulin in those not achieving target with basal insulin. New evidence suggests that pioglitazone may benefit recurrent ischemic events after stroke, although the study was conducted in non-diabetic, insulin-resistant elderly, and adverse events included an increase in fracture risk (Kernan. N Engl J Med 2016;374:1321-31). The good news is that management practices have already improved over the past decade, with more treatment options.

In summary, individualized therapy in elderly people with Type 2 diabetes is especially important given higher rates of adverse consequences from hypoglycemia, renal impairment, and frailty. We hope that future studies will provide more data about optimal strategies for this growing group of patients.

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

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1. Which of the following benefits have not been shown with sodium glucose cotransporter (SGLT)-2 inhibitor treatment of Type 2 diabetes patients?  
   a. renoprotection  
   b. weight loss  
   c. improvement in diabetes dementia  
   d. decreased cardiovascular mortality

2. In the Edinburgh Type 2 Diabetes Study, all of the following were determined to be risk factors for dementia in diabetics, except _______.  
   a. vitamin D deficiency  
   b. smoking history  
   c. elevated HbA1c  
   d. history of cerebrovascular accident

3. Observational data have shown a ~20-25% higher prevalence of cardiovascular complications in diabetes patients whose anti-hyperglycemic treatment was not advanced when needed.  
   a. true  
   b. false

4. Which of the following effects is not observed after bariatric surgery, based on data presented as the 2016 EASD meeting?  
   a. decreased microvascular complications  
   b. weight loss  
   c. increased heart failure  
   d. decreased progression to diabetes in prediabetic patients

5. BioChaperone™ lispro and faster aspart are two investigational meal time insulins that use an excipient that facilitates faster disassociation and absorption once administered subcutaneously.  
   a. true  
   b. false

6. Diabetic ketoacidosis during treatment with SGLT-2 inhibitors has been observed in patients with Type 1 diabetes, but not Type 2 diabetes?  
   a. true  
   b. false

7. Which of following statements is true regarding insulin glargine U-300 and insulin degludec?  
   a. These insulins are superior to traditional insulins with respect to HbA1c lowering and weight loss.  
   b. Each has been associated with a lower incidence of nocturnal hypoglycemia when compared to other basal insulins.  
   c. Several head-to-head trials have been published evaluating their comparative efficacy.  
   d. They are far less expensive than previously available basal insulins

8. Which of the following statements is false?  
   a. Hypoglycemia has been associated with cardiovascular events, but it has not been definitely proven to cause events.  
   b. Sulfonylureas and insulins are typically the drug classes associated with the highest rates of drug-induced hypoglycemia.  
   c. SGLT-2 inhibitors and GLP-1 receptor agonists are associated with low rates of hypoglycemia.  
   d. The ADA-EASD generally recommends strict HbA1c targets regardless of a patient’s age or renal function.

9. Fully integrated closed loop technology involving implanted glucose sensors and bihormonal (insulin and glucagon) pumps are finally available to patients for routine use.  
   a. true  
   b. false

10. In the EMPA-REG OUTCOME trial, the SGLT-2 inhibitor improved renal outcomes. The risk reduction in the composite renal outcome was solely driven by the effect on macroalbuminuria.  
   a. true  
   b. false

11. Which of the below choices it not typically considered a component of 3-point MACE in cardiovascular trials?  
   a. non-fatal myocardial infarction  
   b. heart failure hospitalization  
   c. cardiovascular mortality  
   d. non-fatal stroke

12. It has been recently demonstrated that initial combined anti-hyperglycemic therapy reduces long-terms complications of diabetes versus sequential combination therapy.  
   a. true  
   b. false

13. Based on the data presented by Bjerg from Denmark, the majority of patients with Type 1 diabetes have at least one microvascular complication. Which of the following is not currently categorized as a microvascular complication?  
   a. nephropathy  
   b. retinopathy  
   c. neuropathy  
   d. pulmonary dysfunction

14. In the SUSTAIN-6 trial, the GLP-1 receptor agonist semaglutide was associated with an increased risk of pancreatitis.  
   a. true  
   b. false

15. In the SUSTAIN-6 trial, the GLP-1 receptor agonist semaglutide significantly reduced which of the following cardiovascular events?  
   a. non-fatal stroke  
   b. non-fatal myocardial infarction  
   c. all-cause mortality  
   d. incidence of retinopathy

16. Individualized therapy in elderly people with Type 2 diabetes is especially important given higher rates of adverse consequences from hypoglycemia, renal impairment, and fragility.  
   a. true  
   b. false

17. Which of the following are two outcomes commonly associated with GLP-1 receptor agonists?  
   a. decreased HbA1c, hypoglycemia  
   b. improved lipid profile, weight gain  
   c. hyponatremia, weight loss  
   d. decreased HbA1c, weight loss

18. Which two GLP-1 receptor agonists have now been demonstrated to reduce cardiovascular events in high-risk patients with Type 2 diabetes?  
   a. exenatide and albiglutide  
   b. liiraglutide and semaglutide  
   c. exenatide and dulaglutide  
   d. albiglutide and lixisenatide

19. It is generally felt that the cardiovascular benefit from select glucose-lowering agents is directly the result of improvements in HbA1c.  
   a. true  
   b. false

20. Steatosis in patients with diabetes can lead to which of the following complications?  
   a. cirrhosis  
   b. hepatocellular carcinoma  
   c. hepatic failure  
   d. all of the above
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.
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: October 2016 to July 31, 2017.

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

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

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

Additional comments: ______________

This CME program is sponsored by Yale School of Medicine, New Haven, CT.