Diabetes 2017

Volume 36

Highlights from the
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Diabetes 2017

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Diabetes**2017**

From the 53rd Annual Meeting of the European Association for the Study of Diabetes

***O**ctober 2017*

Dear Colleague:

Time restraints prevented many of you from attending the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD) which was held a few weeks ago in Lisbon, Portugal. Therefore, we developed ***Diabetes 2017*** so that important information presented at the Conference could be shared with you on a timely basis.

Diabetes 2017, 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 and Merck & Co., Inc.* This booklet contains three ***Diabetes 2017*** 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 2017 to July 31, 2018.

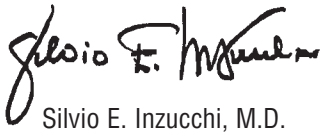
After successfully completing the program, you will be able to:

- 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 17 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

Robert S. Sherwin, M.D.
C.N.H. Long Professor of Medicine
Yale School of Medicine
Director, Yale Diabetes & Endocrinology Research Center



Silvio E. Inzucchi, M.D.
Professor of Medicine
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Director, Yale Diabetes Center

Educational Needs

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

Learning Objectives

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

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
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- 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.goo.gl/6s934t or sent by e-mail to the office of participating physicians. Shortly after the EASD conference concludes, a ***Diabetes 2017*** 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.goo.gl/6s934t. 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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Editors' Summary

In this issue of the ***Diabetes 2017*** monograph, we summarize important new diabetes information that was presented at the *53rd Annual Meeting of the European Association for the Study of Diabetes* (*EASD*) in Lisbon, Portugal.

Following on presentations at the ADA and EASD annual meetings in the past 2 years, data presented at the 2017 EASD meeting provide further evidence of the beneficial cardiovascular (CV) effects from treatment with glucose-lowering drugs. Specifically, data on hospitalizations due to heart failure (HHF) from the EMPA-REG OUTCOME trial of the SGLT-2 inhibitor empagliflozin* and the CVD REAL trial comparing SGLT-2 inhibitors vs. other glucose-lowering agents were presented, as were the primary outcome results with the thiazolidinedione (TZD) pioglitazone in the TOSCA-IT trial and with the GLP-1 receptor agonist (RA) long-acting exenatide in the EXSCEL trial.

Taken together, growing evidence shows that certain glucose-lowering drugs can improve CV outcomes in our patients with Type 2 diabetes.

Hospitalizations due to Heart Failure

Heart failure (HF) is a frequent complication of diabetes, and associated with premature death (~10-fold increased in patients with diabetes and HF vs. diabetes alone [Bertoni *et al*., *Diabetes Care* 2004]). While there is no convincing evidence that glucose control itself has any significant impact on incident HF, there is evidence that a newer class of glucose-lowering medications has a beneficial impact on HF complications.

In the EMPA-REG OUTCOME trial (7,020 Type 2 diabetes patients with Type 2 diabetes with overt CV complications), empagliflozin reduced HHF by 35% (p=0.002), with the benefit consistent irrespective of baseline HbA1c or change in HbA1c (abstract 918), a conclusion supported by results of a computer simulation model of EMPA-REG data (abstract 1133).

Class Effect?

Does the advantage on HHF shown in EMPA-REG apply equally to other drugs in this class? This question was studied in CVD REAL, a large observational study of HHF and all-cause mortality in patients with or without prior cardiovascular disease (CVD) or HF among new users of the three currently available SGLT-2 inhibitors vs. other glucose-lowering agents (abstract 88). Using compiled information from large databases in the US, UK, Sweden, Norway, and Denmark, the CVD REAL investigators reported that use of an SGLT-2 inhibitor, when compared with other diabetes drugs, was associated with significantly reduced risk of HHF in both patients with as well as without prior CVD (HR 0.69 [95% CI 0.59-0.80] and 0.55 [0.34-0.88], respectively) and in both patients with as well as without prior HF (HR 0.68 [0.57-0.81] and 0.55 [0.39-0.77]).* Similar results were observed for all-cause mortality.* Notably, the findings were consistent across the countries in which there was variable use of the 3 currently available SGLT-2 inhibitors, suggesting a class effect for at least these outcomes. Of note, however, the CVD REAL data don't fully agree with the CANVAS study's report of no significant effect on mortality with canagliflozin (HR=0.87; 95% CI: 0.74-1.01) reported earlier this year at the ADA Scientific Sessions.

SGLT-2 Inhibitors vs. GLP-1 Receptor Agonists

In a symposium entitled, "Cardiovascular Complications of Diabetes: Hot Topics", Dr. Stefan Anker, Professor of (Tissue) Homeostasis in Cardiology and Metabolism at Charitė, Berlin, Germany showed evidence across trials, noting that SGLT-2 inhibitor is superior to GLP-1 RAs with regard to reducing risk of HHF. As compared to the 33%-35% reduction in HHF with SGLT-2 inhibitor (EMPA-REG, CANVAS), the outcome (vs. placebo) was -13% (95% CI: 0.73-1.05) with liraglutide* in LEADER and +11% (95% CI: 0.77-1.61) with semaglutide* in SUSTAIN-6, neither finding statistically significant.

Differential CV Effects of GLP-1 Receptor Agonists

The mechanism by which certain GLP-1 receptor agonists confer CV benefits is certainly deserving of further study, since there appears to be significant heterogeneity within the class. As compared to significant, favorable effects on 3-point MACE from liraglutide (in LEADER) and semaglutide (in SUSTAIN-6), lixisenatide* (in ELIXA) and long-acting exenatide (in EXSCEL) had no CV effect.*

CV Effects of Pioglitazone

The TZD pioglitazone has been shown to not only slow atherosclerosis in both the coronary circulation (PERISCOPE trial [Nissen *et al. JAMA* 2008]) and cerebral circulation (CHICAGO [Mazzone *et al. JAMA* 2006]), but also reduce atherosclerotic events in high-risk patients (PROactive trial [*Lancet* 2005]). And last year, IRIS trialists reported that pioglitazone reduced myocardial infarction (MI) and stroke in non-diabetic individuals with insulin resistance and prior stroke or transient ischemic attack (*N Engl J Med* 2016).*

TOSCA-IT compared the effects of pioglitazone (15-45 mg/day) vs. sulfonylureas (SUs), each combined with background metformin, on a composite primary CV outcome of all-cause death, non-fatal MI (including silent MI), non-fatal stroke, and urgent coronary revascularization. There was no difference between treatment arms for the primary CV composite, which occurred in 105 (6.8%) and 108 (7.2%) patients in the pioglitazone and SU arms, respectively (HR=0.96 [95% CI: 0.74-1.26, p=0.79] vs. SUs). Of note, TOSCA-IT had several methodological limitations, including ultimately being underpowered. Also, it was unblinded and had a larger than usual study drop-out rate, and an even larger rate of patients discontinuing study drug prematurely, mainly due to concerns about bladder cancer, that were subsequently allayed. In *post hoc* analyses, CV benefit was suggested with the TZD in those who adhered to therapy, however.

We are entering a new era in diabetes care. Recently reported trials have demonstrated very clearly that use of at least SGLT-2 inhibitors (empagliflozin, canagliflozin) and certain GLP-1 RAs (liraglutide, semaglutide) in high-risk patients confers CV benefits on top of standard-of-care. Findings of these trials will almost certainly be 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 2017***.

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

Diabetes2017

From the 53rd Annual Meeting of the European Association for the Study of Diabetes ■ Lisbon, Portugal

2014 2015 2016 **2017** 2018 2019 2020

Sponsored by **Yale School of Medicine**,
Department of Internal Medicine, Section of Endocrinology

Volume **36** ■ September 13, 2017 ■ Issue **1**

More on the SGLT-2 Inhibitors

The SGLT-2 inhibitors are the newest drug category for the management of patients with Type 2 diabetes. They lower blood glucose concentrations (and HbA1c) by decreasing glucose reabsorption in the proximal nephron, inducing glucosuria. This class is somewhat unique in that it does not require insulin to exert its effectiveness, and can therefore be just as effective in newly-diagnosed patients (who tend to have insulin secretory capacity that is somewhat preserved) as in later-stage patients (where insulin secretion is severely diminished). Added benefits include modest reductions in body weight and blood pressure. Their mechanism of action also explains the SGLT-2 inhibitors' main side effects, which include genital infections (predominately yeast), polyuria, dehydration, and, rarely, acute kidney injury (AKI) and diabetic ketoacidosis (DKA). Recently, a surprising adverse effect was reported with canagliflozin in the CANVAS trial (see *Diabetes 2017*, Volume 35, Issue 3). Therein, the rate of lower limb amputations was nearly doubled in those randomized to the SGLT-2 inhibitor. The reason for this is not clear and has not been reported with other members of this class, dapagliflozin and empagliflozin.

There has been intense interest in this category, stemming from the surprising results from the EMPA-REG OUTCOME trial, initially reported at the EASD two years ago (see *Diabetes 2015*, Volume 32, Issue 3). In that study, which involved more than 7,000 patients with Type 2 diabetes and established cardiovascular disease (CVD), the group assigned to empagliflozin experienced 38%, 32%, and 35% reductions in the hazard rate for cardiovascular (CV) mortality, all-cause mortality, and hospitalization for heart failure (HHF).* The mechanisms behind these striking benefits remain unknown, with theories ranging from simply a diuretic effect, to direct activity within cardiac myocytes, to small increases in circulating concentrations of ketones, which are a more efficient fuel source for the heart.

In addition to the cardiac benefits, empagliflozin was subsequently reported to reduce the progression of chronic kidney disease (CKD)* by 39%—a benefit that included doubling of creatinine and the development of end-stage renal disease (ESRD). There appears to be greater consensus about the mechanisms behind the renal effects of SGLT-2 inhibitors, with most experts pointing to normalization of tubulo-glomerular feedback, with decreased afferent arteriolar blood flow and consequent reduction in glomerular barotrauma. Interestingly, all patients experience a small drop in eGFR initially, related to hemodynamic effects, but then with subsequent stabilization.

In June at this year's *ADA Scientific Sessions* in San Diego, CA, (*Diabetes 2017*, Volume 35, Issue 3) the CANVAS investigators reported that canagliflozin had similar benefits on HHF and CKD, but no significant reduction in CV or all-cause death.* Moreover, there were new adverse effects disclosed, i.e., the aforementioned lower limb amputations and a more modest increase in bone fractures.

The third SGLT-2 inhibitor, dapagliflozin, is still undergoing its own CV outcome trial, DECLARE, with results anticipated in 1-2 years. A fourth member, ertugliflozin,* is still investigational; its CV outcome trial (VERTIS-CV) may also be available during the same time frame. So, within the next 2 years, we should have much more data with this class to better understand how these drugs may differ. Suffice it to say, however, that EMPA-REG specifically—and to a lesser extent CANVAS—have both opened up new avenues of clinical investigation as endocrinologists, cardiologists, and nephrologists try to understand the biological underpinnings of the drugs' CV and renal benefits.

At this week's EASD meeting in Lisbon, dozens of presentations further explored both the benefits and the risks of this emerging glucose-lowering drug category.

EMPA-REG Update: Does HbA1c Matter?

Woerle and the EMPA-REG investigators examined the influence of glycemic control in the trial on heart failure (HF) benefits (abstract 918). In brief, patients were randomized to one of two

doses of empagliflozin (10, 25 mg) or placebo on top of standard-of-care and followed for about 3 years. Background diabetes therapy could be adjusted to achieve local HbA1c targets but only after the first 12 weeks. The mean age of participants was 63 years, with almost half already on insulin therapy. About 75% of patients had coronary artery disease, with nearly half having experienced a previous myocardial infarction (MI). Almost 25% had had a prior stroke, and about 10% had pre-existing HF. The baseline HbA1c was 8.1%, with reasonably good control of other CV risk factors, e.g.,-- blood pressure and lipids. Evidence-based CV therapies were used extensively, with approximately 8 out of 10 patients taking a statin; similar proportions of patients were taking a renin-angiotensin system (RAS) blocker and aspirin.

In this post-hoc analysis from the trial, the frequencies of HHF were analyzed in the pooled empagliflozin group vs. placebo in three ways:

(1) by baseline HbA1c (<7.0%, 7.0 to <8.0%, 8.0 to <9.0%, and ≥9.0%);
(2) by time-dependent change in HbA1c during the entire trial (≥0.5% vs. <0.5%); and
(3) by reduction in HbA1c from baseline to week 12 (≥0.5% vs. <0.5%).

Differences in risk between the two treatment groups were then assessed using a Cox proportional hazards model.

The investigators found that the benefit of empagliflozin on HHF was consistent irrespective of baseline HbA1c or change in HbA1c (Figure 1). These data suggest that the reduction in HHF is unrelated to the baseline glycemic status of the patient or to the drug's effect on glycemia. Similar data (abstract 916) were also presented by the same group of investigators in an examination of the outcome of CV death, but this was an encore of a presentation at the ADA in San Diego (see *Diabetes 2017*, Volume 35, Issue 2). Both sets of data are provocative and seem to imply that the CV benefits of this glucose-lowering drug has little to do with glucose-lowering.

Figure 1. No Effect from HbA1c Changes on Rates of Hospitalization for Heart Failure (HHF) in the EMPA-REG OUTCOME trial

	n with HHF/n Analyzed (%)				*Treatment by subgroup interaction*
	Empagliflozin	*Placebo*	*HR (95% CI)*	*HR (95% CI)*	
HHF during the trial					
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)		
HbA1c at baseline					p=0.8875
<7.0%	10/297 (3.4)	7/127 (5.5)	0.56 (0.21, 1.48)		
7.0 - <8.0%	56/2042 (2.7)	43/1029 (4.2)	0.66 (0.44, 0.98)		
8.0% - <9.0%	30/1534 (2.0)	27/795 (3.4)	0.56 (0.34, 0.95)		
≥9.0%	29/812 (3.6)	18/382 (4.7)	0.76 (0.42, 1.37)		
HHF after week 12					
All patients	121/4656 (2.6)	85/2303 (3.7)	0.70 (0.53, 0.93)		
HbA1c change from baseline at week 12					p=0.5418
Reduction of ≥0.5%	53/2333 (2.3)	18/497 (3.6)	0.62 (0.36, 1.07)		
Reduction of <0.5%	67/2321 (2.9)	67/1806 (3.7)	0.76 (0.54, 1.07)		

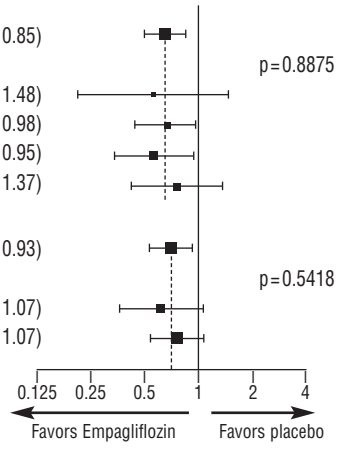
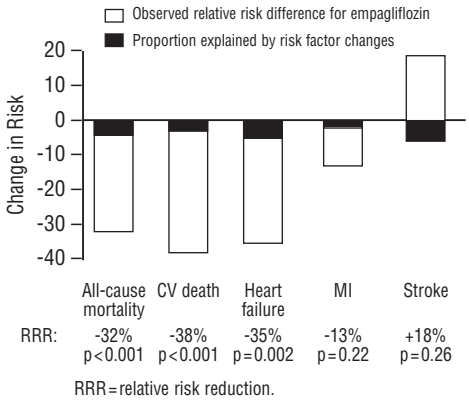


Figure 2. Observed Risk Reductions and Proportions Attributable by Simulation to Conventional Cardiovascular Risk Factors



RRR=relative risk reduction.

The investigators concluded that empagliflozin-associated changes in conventional CV risk markers in the trial appear to explain only a minor proportion of the actual risk reductions in key endpoints. The inference, of course, is that alternative mechanisms are likely at play.

Such a conclusion was also supported by a computer simulation model of the EMPA-REG data, reported by Coleman *et al*. from the UK, Canada, and Germany (abstract 1133). The model was used to estimate 3-year CV event rates utilizing patient-level information from the trial, including baseline HbA1c, systolic BP, lipids, eGFR, WBC count, and hemoglobin concentrations, prevalence of albuminuria, atrial fibrillation, and smoking, and prior history of ischemic heart disease, MI, stroke, HF, renal failure, amputation, and blindness. Estimated absolute event rates for participants randomized to empagliflozin or placebo were used to calculate modeled CV relative risk reductions (RRRs) Figure 2). Compared to the observed RRRs in the actual trial, the simulation suggested that the SGLT-2 inhibitor would reduce the risk of all-cause mortality by just 4% (~13% of the 32% RRR observed), CV mortality by just 3% (~8% of the 37% RRR observed), HHF by 5% (~15% of the 35% RRR observed), MI by 2% (compared with the non-significant 13% RRR observed), and stroke by 6% (compared with the non-significant 18% RRR increase observed).

Using data from the UK Primary Care Clinical Practice Research Datalink, Shields and coworkers conducted a study to determine predictors of response to SGLT-2 inhibitors and DPP-4 inhibitors, both now common second-line therapies used to treat Type 2 diabetes (abstract 873). In regression models, the investigators found that associations between eGFR and 6-month response to SGLT-2 inhibitors and DPP-4 inhibitors go in opposite directions: Higher eGFR was associated with a lesser response to DPP-4 inhibitors but a better response to SGLT-2 inhibitors ($p<0.0001$). Likewise, greater BMI and triglycerides were associated with a lesser response to DPP-4 inhibitors compared with SGLT-2 inhibitors ($p<0.001$ for both BMI and triglycerides). For both DPP-4 inhibitors and SGLT-2 inhibitors, greater baseline HbA1c ($p<0.0001$ for both) and shorter duration of diabetes ($p<0.001$ for both) were associated with a greater reduction in HbA1c at 6 months. These preliminary analyses identify simple criteria that may aid treatment decisions in Type 2 diabetes.

As noted above in the HbA1c-based presentations by the EMPA-REG investigators, HbA1c change does not appear to have any appreciable influence on the effects of that SGLT-2

inhibitor on CV death or HHF. Accordingly, it remains unclear, at least from a CV standpoint, what these modest differences between the drug categories actually mean.

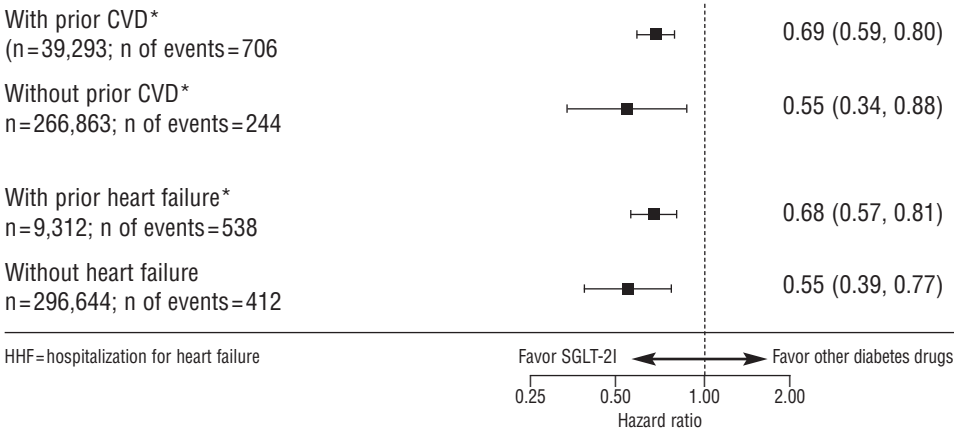
Class Effect?

Do the advantages shown in EMPA-REG apply equally to other drugs in this class? Well, CANVAS showed that some, but not all, appear to apply to canagliflozin. In a large observational study, CVD REAL, Cavender and international colleagues reported on HHF and all-cause mortality in patients with or without prior CVD or HF among new users of the three currently available SGLT-2 inhibitors vs. other glucose-lowering agents (abstract 88). They compiled the information from large databases in the US, UK, Sweden, Norway, and Denmark. Canagliflozin was the most common member of the class used in the US whereas dapagliflozin tended to be used more commonly in Europe. Hazard ratios were calculated by country and pooled for a weighted average. After propensity matching, baseline characteristics were balanced between groups. A total of 306,156 patients with >150,000 patient-years of follow-up was analyzed, with 950 new HHF events recorded. Use of an SGLT-2 inhibitor, when compared with other diabetes drugs, was associated with significantly reduced risk of HHF in both patients with as well as without prior CVD (HR 0.69 [95% CI 0.59-0.80] and 0.55 [0.34-0.88], respectively) and in both patients with as well as without prior HF (HR 0.68 [0.57-0.81] and 0.55 [0.39-0.77]) (Figure 3).* Similar results were observed for all-cause mortality.* Notably, the findings were consistent across the countries in which there was variable use of the 3 currently available SGLT-2 inhibitors. So, these data do suggest a class effect for at least these outcomes. The CVD REAL data don't fully agree with the CANVAS study's report of no significant effect on mortality with canagliflozin. The reason for this discordance is not clear. It may reflect differences in the populations, other confounders not controlled for in the observational study, or simply variations around confidence intervals that perhaps should not be over-interpreted.

Safety Concerns

Safety data from dapagliflozin clinical trials were presented by Scheen and colleagues from the US and Europe (abstract 905). Data were analyzed from three pools of trials: (1) 13 placebo-controlled trials of up to 24 weeks in length (dapagliflozin, n=2360; placebo, n=2295); (2) 21 larger placebo- or comparator-controlled trials of up to 208 weeks in duration (dapagliflozin, n=5936; control, n=3403), in order to detect differences in the rare adverse event of DKA; and (3) 30 placebo- or comparator-controlled trials of at least 12 weeks duration to assess for differences in the incidence of lower limb amputations (dapagliflozin, n=9195; control, n=4629) .

Figure 3. CVD REAL: Pooled Hazard Ratios for HHF in Patients With and Without Established CVD or Heart Failure at Initiation of the Index Diabetes Drug



Overall, genital infections were more common in the dapagliflozin-treated patients (6% vs. 1 %), but adverse events and serious adverse events were similar between the two groups (dapagliflozin 60% and 5% vs. placebo 56% and 5%, respectively). Specifically, the incidence of hypoglycemia, volume depletion events, urinary tract infection, fractures, and amputations were not different. In the 21-study pool, 1 serious DKA event and 3 events described as "ketonuria/metabolic acidosis" occurred with dapagliflozin (for an estimated incidence for any ketotic event of 0.03%) and none in the comparator/placebo group.

The risk of DKA is clearly low when this drug class is used in Type 2 diabetes. Nonetheless, we advise using SGLT-2 inhibitors cautiously in the more insulin-deficient phenotypes, such as in lean individuals with long-standing disease, especially when there is any suspicion of latent autoimmune diabetes of adults (LADA). In Type 1 diabetes, we do not generally endorse their off-label use. Here, the risk of DKA and other ketone-related adverse events may be as high as nearly 10%. This observation has to some degree dampened enthusiasm in research circles for testing SGLT-2 inhibitors in Type 1 diabetes, although they actually do improve glycemic control and also lead to a reduction in insulin doses.

The origin of DKA after SGLT-2 inhibition is not completely understood. Multiple mechanisms may be at play. These include a reduction in insulin dose, which may decrease the suppression of lipolysis and result in higher circulating levels of free fatty acids, the substrate for ketone production. Also, an increase in glucagon secretion from pancreatic alpha cells has been reported; this may promote not only an increase in endogenous glucose production but also an increase in ketogenesis. Finally, a decrease in ketone clearance has also been observed in animal models of SGLT-2 inhibition. Interestingly, when it occurs, SGLT-2 inhibitor-associated DKA often presents with much lower glucose levels than are typically seen in ordinary DKA (presumably due to ongoing augmented urinary glucose losses).

Renal function poses another theoretical concern with this class, given the osmotic diuresis that the drugs induce. In fact, as noted previously, long-term clinical trials actually indicate preservation of renal function and decreased risk of CKD progression. Nonetheless, post-marketing reports about AKI episodes have led to FDA warnings about this possibility. To further explore this issue, Agarwal and international colleagues analyzed pooled safety data from >12,000 patients with Type 2 diabetes who were randomized to two doses of empagliflozin or placebo across 19 clinical trials (abstract 904). Acute renal failure (ARF) and AKI as adverse events were found to occur with equal frequency between the groups (Table 1).

Despite these data, we continue to feel that extra caution is advisable when using SGLT-2 inhibitors in those with mild-moderate CKD, especially in patients prone to volume depletion and on top of other drugs that affect glomerular blood flow, such as RAS blockers and NSAIDs. Note also that SGLT-2 inhibitors are not indicated in patients with eGFR <45-60 ml/min/1.73m^2 (depending on the specific drug), although,

interestingly, in EMPA-REG OUTCOME both the CV and CKD protective effects appeared to extend to those with eGFR 30-45 ml/min/1.73m^2.

Combination Therapy

Given the aforementioned increase in pancreatic glucagon secretion by SGLT-2 inhibitors, and the tendency for incretin-based therapies to suppress glucagon, might their combined use have a particular metabolic advantage? In a study presented this week, Bonner and French colleagues (abstract 888) used histology and quantitative PCR to examine the *ex-vivo* effects of dapagliflozin and the GLP-1 receptor agonist, liraglutide, alone and in combination using human and murine pancreatic tissue. In both models, co-exposure to liraglutide did indeed decrease the normally augmented glucagon expression induced by dapagliflozin at a normal ambient glucose concentration of 6 mM (about 108 mg/dL). The investigators suggested that this specific combination might therefore have unique benefits in terms of glucose-lowering.

Such a study was actually presented this week. Martinez and US colleagues randomized 24 patients with Type 2 diabetes and suboptimal control (HbA1c 8.3 ± 0.4%) on metformin with or without a sulfonylurea to either canagliflozin (300 mg/day; n=8), liraglutide (1.8 mg/day; n=8), or both drugs (n=8) for 16 weeks (abstract 882). Baseline characteristics were similar across the three groups. Testing included the usual glycemic and anthropometric parameters, with calculation of the insulinogenic index (a measure of beta-cell function) and the disposition index (another measure of insulin secretion but incorporating the degree of insulin resistance as well). Combination therapy led to additional benefits on body weight, glycemic control, beta-cell function, as well as systolic blood pressure (Table 2). The collaborators proposed that their data provide strong rationale for the combined use of SGLT-2 inhibitors and GLP-1 receptor agonists in patients with Type 2 diabetes who require better control after conventional agents.

These data do show greater benefits with combination therapy. The effects on weight, SBP, and insulin secretion suggest actual synergy. However on the main glycemic parameter of HbA1c, the results appear less than additive.

Guja *et al.* from Romania and the US completed a 24-week extension trial of DURATION-8, which assessed efficacy and safety of combination exenatide ER (2 mg subcutaneous weekly) plus dapagliflozin (10 mg po daily) versus exenatide ER/placebo versus dapagliflozin/placebo in a randomized, double-blind fashion (abstract 6). Outcome measures included glycemic control (HbA1c, fasting plasma glucose [FPG], 2-hour postprandial glucose [2h-PPG]), body weight, and SBP at baseline and week 52. Combination therapy resulted in greater reductions in each of the aforementioned parameters than either drug as monotherapy, but, as with the previous abstract, the HbA1c effect was less than additive. For example, HbA1c was only -0.37% better with combination therapy vs. exenatide alone and only -0.52% better than dapagliflozin alone (both p<0.001). Serious adverse events and minor hypoglycemia occurred at rates of 4.8% and 1.3% in the combination therapy group, at 5.2% and 0% in exenatide monotherapy, and at 5.2% and 0.4% with dapagliflozin monotherapy. From these data, the investigators concluded that combination therapy is well tolerated without unanticipated adverse effects and provides sustained improvement in glycemic control, weight reduction, and SBP over 52 weeks.

Is the high cost of this combination of two branded products (approximately $1000 per month) worth it? There also are no data as to whether combined therapy might mitigate the risk of DKA (given the suppression of glucagon with the GLP-1 receptor agonist). Also, no data are available as to whether combination therapy could augment the already demonstrated CV benefits of each class.

While the benefits of SGLT-2 inhibitors for the heart and kidneys are notable, we would caution proper patient selection and, despite the CVD REAL findings, it should be emphasized that the advantages in patients *without* prevalent CVD or CKD have not yet been demonstrated in randomized clinical trials.

Table 2. Effects of Liraglutide ± Canagliflozin on Body Weight, Glycemic Control, Beta-cell Function, and Blood Pressure

Variables	*Liraglutide*	*Canagliflozin*	*Combination*	*p-value*
Body weight (kg)*	-2.6±1.4	-3.4±0.6	-7.2±1.2	0.01
Systolic blood pressure (mmHg)*	0±7	-6±3	-16±3	0.04
HbA1c (%)	-1.59±0.54	-1.10±0.32	-1.94±0.49	0.39
Fasting plasma glucose (mg/dl)†	-44±15	-32±13	-76±24	0.18
Mean OGTT plasma glucose (mg/dl)†	-84±15	-75±14	-134±23	0.04
Insulinogenic index (ΔI/ΔG)†	+0.58±0.18	+0.17±0.11	+0.93±0.40	0.05
Disposition index†	+0.73±0.20	+0.67±0.25	+1.26±0.26	0.05

*Combination is more than additive; † Combination is additive, ‡ Corrected for glycosuria; OGTT=oral glucose tolerance test, ANOVA method used to calculate p-value.

Table 1. Acute Renal Failure/Acute Kidney Injury Adverse Events by eGFR

	Placebo		*Empagliflozin 10 mg*		*Empagliflozin 25 mg*	
	n/n (%)	*Rate/100-patient years*	*n/n (%)*	*Rate/100-patient years*	*n/n (%)*	*Rate/100-patient years*
All patients*	159/4203 (3.8)	2.19	137/4221 (3.2)	1.78	141/4196 (3.4)	1.84
eGFR ≥90	13/1172 (1.1)	0.71	9/1204 (0.7)	0.45	10/1233 (0.8)	0.49
eGFR 60 to <90	56/2298 (2.4)	1.42	56/2285 (2.5)	1.35	53/2216 (2.4)	1.30
eGFR 45 to <60	55/529 (10.4)	5.22	45/530 (8.5)	3.96	42/531 (7.9)	3.72
eGFR 30 to <45	32/197 (16.2)	7.87	24/192 (12.5)	6.23	34/197 (17.3)	8.86
eGFR <30	3/7 (42.9)	37.65	3/9 (33.3)	21.35	2/16 (12.5)	7.59

* Baseline eGFR subgroups (mL/min/1.73m^2) according to MDRD (Modification of Diet in Renal Disease) formula. Baseline eGFR measurements available for 12,616 participants (Placebo, n=4203; Empagliflozin 10 mg, n=4220; Empagliflozin 25 mg, n=4193). Renal safety profile was assessed using investigator-reported AEs. ARF was assessed based on the narrow standardized MedDRA query for the condition, which included the MedDRA preferred term AKI.

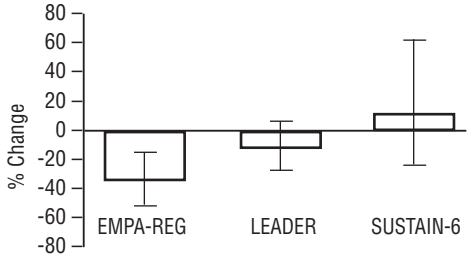
Diabetes and CVD

Patients with Type 2 diabetes have a 2- to 4-fold increased risk of complications related to atherosclerosis, including CV (myocardial infarction, unstable angina, HF, and CV death), cerebrovascular (stroke, TIAs), and peripheral vascular events. In addition to hyperglycemia, the mechanisms linking diabetes to atherosclerosis are multiple, including obesity, insulin resistance, dyslipidemia, hypertension, inflammation, and hypercoagulability.

Thus, it comes as no surprise that the Puccini Hall at the Lisbon Convention Center was filled to capacity this morning based on attendees' great interest in the EASD/ESC Symposium "Cardiovascular Complications of Diabetes: Hot Topics". Dr. Stefan Anker, Professor of (Tissue) Homeostasis in Cardiology and Metabolism at Charité Berlin, Germany, discussed "Heart Failure in Diabetes". By way of background, HF is one CV complication of diabetes getting an increasing amount of attention, owing to its frequency and its association with premature death (~10-fold increased in patients with diabetes and HF vs. diabetes alone [Bertoni *et al., Diabetes Care* 2004]). Interestingly, there is no convincing evidence that glucose control itself has any significant impact on incident HF. In contrast, increasingly recognized is the impact of glucose-lowering medications on HF complications, some having either beneficial (SGLT-2 inhibitors, perhaps metformin),* neutral (insulin, sulfonylureas, and probably GLP-1 agonists), or adverse effects (TZDs, certain DPP-4 inhibitors). It should be noted that other interventions, specifically reducing blood pressure (BP) and the use of certain CV medications, reduce the incidence of HF in those with diabetes as much as those without.

Anker focused his discussion on SGLT-2 inhibitors and the CANVAS (canagliflozin) and EMPA-REG (empagliflozin) trials. A pre-specified, hierarchical approach to data analysis was followed in CANVAS. The primary endpoint of 3-point major adverse cardiovascular events (MACE; i.e., death from CV causes, non-fatal MI, or non-fatal stroke) reached statistical significance, with 14% decreased risk with canagliflozin vs. placebo (HR=0.86, 95% CI: 0.75 -0.97; p<0.001 for non-inferiority, p=0.02 for superiority), however, the second endpoint in the sequential analyses, all-cause mortality, did not (HR=0.87; 95% CI: 0.74-1.01) [Neal *et al., NEJM* 2017].* Therefore, analysis of HHFs became exploratory, with a favorable effect realized with the SGLT-2 inhibitor (HR=0.67; 95% CI: 0.52-0.87). Among the 14% of patients with a history of HF (not an inclusion criterion of the study), the results were consistent (p for interaction=0.51), although the analysis was not pre-specified. Interestingly enough, there was a statistically significant benefit, favoring SGLT-2 inhibitor, in the prespecified analyses of the primary endpoint in those taking beta-blockers or diuretics.

Figure 4. HHF in EMPA-REG (empagliflozin), LEADER (liraglutide), and SUSTAIN-6 (semaglutide)



HHF=hospitalization for heart failure
Satta *et al., JACC 2017*

As noted on page 1, in the EMPA-REG trial of Type 2 diabetes patients with established CVD, the group assigned to empagliflozin experienced 35% reduction in the hazard for HHF, with the benefit observed in both the 10 mg dose group (HR=0.62, 95% CI: 0.45-0.86) and the 25 mg dose group (HR=0.68, 95% CI: 0.50-0.93). Benefit of treatment in the ~10% of patients with HF (not an inclusion criterion of the study) was similar to that in patients without HF. Dr. Anker showed evidence across trials (Figure 4), noting that SGLT-2 inhibitor is superior to GLP-1 agonists with regard to reducing risk of HHF.*

The speaker concluded his presentation by noting that these important results from the field of diabetes research have stimulated additional investigative efforts in cardiology, mainly in the field of HF. He specifically summarized 3 major trials—DAPA-HF trial of dapagliflozin and the EMPEROR-Reduced and EMPEROR-Preserved trials of empagliflozin—that are underway to study the impact of SGLT-2 inhibition in different HF populations with reduced or preserved left ventricular ejection fraction. More than 10,000 patients will be recruited into these trials over the next several years. If the results of CANVAS and EMPA-REG can be confirmed, treatment of diabetes in patients with HF will most certainly change accordingly. Moreover, since all these trials are recruiting non-diabetic individuals as well, the benefits of this class may also extend to those individuals.*

Dr. Peter Grant, Professor, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK, discussed "Interactions Between Diabetes and Thrombotic Mechanisms that Promote CV Damage". As the backdrop to his presentation, Dr. Grant reminded attendees that diabetes is characterized by a higher risk of occlusive, thrombotic CVD with poorer outcomes than are seen in patients without diabetes. He provided evidence that glycation of coagulation proteins in poorly-controlled diabetes interferes with normal function, leading to pro-thrombotic changes and resultant clot formation as well as decreased clot lysis, both of which contribute to CVD. In this regard, components of the coagulation cascade are affected: increased production of coagulation proteins (thrombin, fibrinogen) and fibrin clot formation; decreased fibrinolysis (plasmin, PAI-1, tPA) and fibrin breakdown, leading to decreased clot remodeling; and proinflammatory changes within the fibrin clot leading to platelet adhesion/aggregation.

Grant first discussed the role of thrombin, the primary activator of platelets, which has pro-thrombotic, vasoconstrictive, and pro-inflammatory effects. Increased production of thrombin is seen in diabetes, notably after hypoglycemia, and with longer duration of diabetes, macrovascular disease, and microalbuminuria. Given the complex interaction that thrombin has with the vasculature, diabetes patients are at greater propensity towards the platelet activation, hypercoagulability, and the inflammatory processes that thrombin initiates. Glycation of fibrinogen leads to generation of dense, tightly packed fibrin structure that is more resistant to clot lysis. Glycation of plasminogen and increased PAI-1 lead to inhibition of clot lysis. Furthermore, glycation promotes the release (level and volume) of activated immature, reticulated platelets into the circulation, which are more likely to participate in thrombosis (and are aspirin/clopidogrel resistant). With regard to mechanism, Grant reviewed a recent paper by Kraakman *et al.* (*J Clin Invest* 2017): Hyperglycemia appears to stimulate Kupffer cells in the liver, leading to increased production of thrombopoietin in the marrow, which in turn stimulates the increased production and release of reticulated platelets. The same research group showed that the amelioration of glycemia reduces Kupffer cell mass, thrombopoietin level, and reticulocyte count,

through the RAGE receptor. Taken together, the strongly prothrombotic milieu generated by diabetes contributes to both artheroma formation and intra-arterial thrombus.

Several other presentations at this week's EASD annual meeting were noteworthy and extended our understanding of the important association between diabetes and CVD.

Ollgaard and Danish investigators presented new data from the multifactorial Steno-2 study on HF outcomes (abstract 85). Herein, 160 patients with Type 2 diabetes and microalbuminuria were randomized to conventional therapy or intensified, multifactorial intervention involving both behavioral and pharmacologic approaches targeting control of HbA1c, BP, and lipids. Treatment included ACE inhibitors or angiotensin II receptor blockers for BP reduction (due to the presence of microalbuminuria) and statins or fibrates for lipid management. See Table 3 for specifics of the interventions employed by the Steno-2 investigators. After 7.8 years, the hazard for overall CV complications was reduced by a striking 53% in the intensive group (HR 0.47 [95% CI, 0.24-0.73; p=0.008]) (Gaede *et al NEJM* 2003). At that point, intensive-therapy was advised to all patients and the study continued as an observational one. For this presentation, the investigators identified HHF with up to 22 years of follow-up from nationwide registries and chart review. Time-to-event rates were compared using Cox-regression, adjusted for age and sex.

Ten original intensive-therapy group patients were hospitalized for HF during the follow-up period vs. 19 patients in the original conventional-therapy group. The unadjusted HR was 0.39 (0.18-0.84, p=0.017) in favor of the intensive group (Figure 5); after adjustments, the HR was 0.37 (0.17-0.81, p=0.013). The data remained significant when accounting for death as a competing risk. Of note, in the HF patients, atherosclerotic CVD had developed in 10 conventional therapy patients vs. just 1 in the intensive therapy group. The investigators concluded that intensified, multifactorial intervention in Type 2 diabetes patients with microalbuminuria reduces the risk of HHF, probably by reducing ischemic HF.

Figure 5. Time to HHF: Follow-up of Steno-2 Type 2 Diabetes Patients with Microalbuminuria

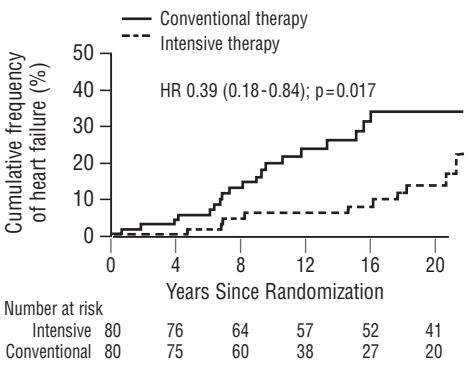


Table 3. Treatment Goals for the Conventional-Therapy Group and the Intensive-Therapy Group During the Evolution of the Steno-2 Trial

	Conventional Therapy		*Intensive Therapy*	
Variable	*1993-1999*	*2000-2001*	*1993-1999*	*2000-2001*
Systolic blood pressure (mmHg)	<160	<135	<140	<130
Diastolic blood pressure (mmHg)	<95	<85	<85	<80
Glycosylated hemoglobin (%)	<7.5	<6.5	<6.5	<6.5
Fasting serum total cholesterol (mg/dl)	<250	<190	<190	<175
Fasting serum triglycerides (mg/dl)	<195	<180	<150	<150
Treatment with ACE inhibitor irrespective of blood pressure	No	Yes	Yes	Yes
Aspirin therapy				
For patients with known ischemia	Yes	Yes	Yes	Yes
For patients with peripheral vascular disease	No	No	Yes	Yes
For patients without coronary heart disease or peripheral vascular disease	No	No	No	yes

* ACE=angiotensin-converting enzyme.

There is also increasing interest in lower limb amputation (LLA) in diabetes due to the aforementioned puzzling recent findings that a popular drug, canagliflozin, increased LLA risk in the CANVAS study. Déruaz-Luyet and US and German colleagues used data from the Truven Health MarketScan databases to calculate the incidence rate of LLA in patients with Type 1 or Type 2 diabetes and a control, non-diabetic group, as well as associated comorbidities prior to the event (abstract 1197). From this database, cases of non-traumatic LLA were found, using both diagnosis and procedure codes, all involving patients without a prior recorded history of amputation. Incidence rates per 1000 person-year (PY) were determined for each cohort and by gender. In addition, reported comorbidities in the month prior to amputation were assessed.

The mean age was 42.8±17.1 years in the controls and 56.8±14.0 in those with diabetes (50.6 in Type 1; 57.8 in Type 2). The groups were relatively equally divided between the genders. Crude overall incidence rates of LLA were 0.08, 5.79, and 1.62 per 1000 PY in the control, Type 1, and Type 2 groups, respectively. In all three cohorts, LLA incidence was about 1.5-2 times greater in men than in women. In the four weeks preceding LLA, compared to controls, patients with diabetes more often had a claim for foot or leg ulcers (73.3% vs. 39.7%), osteomyelitis (65.0% vs. 34.8%), cellulitis (56.5% vs. 29.3%), or Charcot foot (1.8% vs. 0.2%). In contrast, foot deformities were more frequently reported in controls (16.7% vs. 5.4%). Claims for ESRD were more common in the weeks prior to LLA in the Type 1 cohort (29.4%).

For some reason, one atherosclerotic manifestation not increased in patients with diabetes is aortic aneurysm and aortic dissection. So were the findings from Avdic *et al.* from Sweden (abstract 84). They used the Swedish National Diabetes Register, matching each individual with diabetes to 5 population-based control subjects without diabetes found in other national databases. The risk of aortic aneurysm and dissection and subsequent mortality were compared using Kaplan-Meier curves and Cox-regression hazards models.

448,319 individuals with Type 2 diabetes and 2,251,015 controls were found with records between 1998 and 2015. Mean follow-up time was about 7.0 years. There were 2,878 cases of aortic aneurysm and 200 aortic dissections in the diabetic group vs. 16,740 and 2,020, respectively, in the control group. The hazard ratio (HR) in the

diabetic cohort was 0.72 (95% CI 0.68-0.77, p<0.001) for aortic aneurysm and 0.53 (0.42-0.66) for dissection, compared to controls. Adjusted survival rates after either event were actually better in those with diabetes, significantly so following a claim for aortic aneurysm. The investigators concluded that individuals with Type 2 diabetes are at *reduced* risk for aortic aneurysm and dissection. They theorized that glycated cross-links in aortic tissue may play a protective role in the progression of aortic disease in diabetes but offered no data to actually support that contention.

Given the frequency with which our diabetic patients suffer from premature CVD, more research into its nature and preventive strategies is sure to eventually be leveraged to improve their health outcomes.

So Many Posters, So Little Time....

Stiff Hands

Aleppo and American colleagues invited 6,200 adults participating in the T1D Exchange Registry to complete an internet-based survey, inquiring about the diagnosis of cheiroarthropathy (abstract 1196). This is defined as a condition marked by limited joint mobility, sometimes with true flexion contractures, often accompanied by thickening of the overlying skin, and most commonly seen in diabetes, classically in the hands. 1,912 adults (62% female, 90% non-Hispanic White, mean age 40 years, median diabetes duration 20 years, mean HbA1c 7.8%) responded (response rate 32%). Approximately a third (n=586) reported ≥1 joint problem: 50% (293) were diagnosed with frozen shoulder, 50% (293) with trigger finger, and 45% (261) with carpal tunnel, some with multiple joint involvement. Only 16% (92) and 11% (66) were diagnosed with Dupuytren's contracture and limited joint mobility, respectively. Adults diagnosed with joint disease were more likely to be older (mean 53 vs. 34 years; p<0.001) and have longer duration of diabetes (median 35 vs. 16 years; p<0.001). HbA1c was 7.6% and 7.9% for participants with and without cheiroarthropathy, respectively. More than half (333) were treated with physical therapy, half (293) with surgery, and 40% (234) with steroids. Development of standards-of-care for early recognition and treatment of diabetic cheiroarthropathy is needed, particularly for older adults and individuals with long-term diabetes.

Pregnancy and the Eyes

Vambergue and coworkers from France determined the prevalence and progression of diabetic retinopathy during pregnancy in a cohort of 499 Type 1 diabetic pregnancies (mean age 29.7 years; duration of diabetes 13.6 years) followed in the same center from 1997 to 2015 (abstract 1039). Retinal examination was performed each trimester in the absence of retinopathy and each month when retinopathy was observed at first examination. At enrollment, 69.7% of women had normal fundus photography, 23.8% a nonproliferative diabetic retinopathy (NPDR), and 6.4% proliferative diabetic retinopathy (PDR) according to the Early Treatment Diabetic Retinopathy Study (ETDRS) method of categorization. Progression of retinopathy (defined as ≥1 stage of deterioration) occurred in 21.8% of women. The regression rate at 1 year post-partum was 9.3%. Women who demonstrated progression had significantly higher preconceptional, first, and second trimester HbA1c compared to the women without progression. Additionally, decrease in HbA1c was significantly greater between preconception and first trimester, between first and third trimester, and between preconception and the lowest HbA1c during pregnancy among the women with progression. After multivariate analysis, risk factors for retinopathy progression were duration of diabetes >10 years (p<0.0001), nulliparity (p<0.05), and absence of retinopathy before pregnancy (p<0.001). This study highlights the ongoing risk of retinopathy progression during pregnancy among women with Type 1 diabetes, especially among those with the greatest decreases in HbA1c. This may be the direct result of circulating factors that stimulate angiogenesis.

Early Screening for Gestational Diabetes?

Bianchi and associates from Italy evaluated early screening for gestational diabetes mellitus (GDM) in women with obesity, previous GDM, or fasting plasma glucose (FPG) 100-125 mg/dL at the initial prenatal visit, per 2011 Italian guidelines (abstract 948). 1338 consecutive pregnant women underwent a 75g OGTT between January 2013 and December 2015 according to national guidelines; diagnosis of GDM was based on IADPSG/WHO 2013 criteria. 14.4% of screened women were at high risk of GDM (defined as the presence of ≥1 of the following at the initial visit: BMI ≥30 kg/m^2, prior GDM, or FPG 100-125 mg/dL). Of these women, 84.3% had only one major risk factor (41.7% obesity, 34.8% previous GDM, 7.8% high FPG at the first trimester); 7.0% had both previous GDM and obesity, 6.1% had both previous GDM and high FPG, and 2.6% had both high FPG and obesity. None had all 3 major risk factors. Screening between 16th-18th gestational weeks was performed in half of cases, and OGTT was repeated later in pregnancy for 28% of these women due to normal glucose tolerance at the first evaluation.

Among high-risk women, 40% of those with FPG 100-125 mg/dL in the first trimester, 53% of the obese women, and 65% of those with previous GDM underwent an early OGTT. The prevalence of GDM in high-risk women was 67%. Among those performing early screening, GDM was detected in 41% (37/91) of women at the time of first screening and 37% (19/51) at 24th-28th gestational week. Among women performing only late screening, GDM was diagnosed in 74% (66/89) of the cases. GDM was diagnosed at the time of early screening in 56% of the women with previous GDM, 67% of those with obesity, and 80% of those with high FPG at the first trimester. The prevalence of GDM was more common in women with 2 risk factors: 100% in those with obesity and high FPG in the first trimester. On the basis of these data, the investigators suggested that earlier (16th-18th gestational weeks) screening for GDM should be implemented in high-risk women, especially in those with FPG in the range 100-125 mg/dL at first prenatal visit and obesity. It remains to be determined whether early diagnosis and subsequent treatment will actually improve perinatal outcomes.

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

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Diabetes2017

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Singing the Praises of Pioglitazone?: TOSCA-IT

The thiazolidinedione (TZD) drug, pioglitazone, has potent insulin-sensitizing properties. Because insulin resistance is a risk factor for atherosclerosis, the TZDs were initially introduced in the 1990s with great hope that they would prevent CV complications in Type 2 diabetes. As it turned out, the first TZD was taken off the market because of liver toxicity before any CV outcome studies could be performed. The second TZD, rosiglitazone, proved to be neutral for MACE in the RECORD study and was actually once suspected of *increasing* myocardial ischemic events. Which leaves the third (and likely final) TZD, pioglitazone. This glucose-lowering drug has been shown to have anti-atherosclerotic effects in both the coronary (PERISCOPE [Nissen *et al. JAMA* 2008]) and cerebral (CHICAGO [Mazzone *et al. JAMA* 2006]) circulations. In 2006, pioglitazone was shown to reduce MACE by 16% in the PROactive trial involving more than 5,000 patients with established CVD (Dormandy *et al. Lancet* 2005;366:1279-89).* More than a decade later, in 2016, the IRIS trial demonstrated that pioglitazone reduced MI and stroke in non-diabetic individuals with insulin resistance and prior stroke or transient ischemic attack (Kernan *et al. N Engl J Med* 374:1321-31).* Clearly, pioglitazone not only slows atherosclerosis but also reduced atherosclerotic events in high-risk patients, even when glucose levels were not yet in the diabetic range. Unfortunately, the drug has lost much of its luster over the past decade due to its recognized adverse effects: weight gain, edema, increased heart failure risk, and bone fractures. When concerns about possible risk of bladder cancer arose several years ago, prescriptions for the drug plummeted and have never really rebounded, despite follow-up studies that have generally dispelled the cancer concern.

One question that has not been answered is whether pioglitazone prevents CV events in a lower risk population—i.e., as a primary prevention strategy.* This was essentially the question addressed by a randomized clinical trial conducted at 57 centers in Italy, the *Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA-IT)*, results of which were presented at the EASD annual meeting in Lisbon on Wednesday morning. Much of this background was reviewed by the trial's principal investigator, Professor Gabrile Riccardi from the University of Naples Federico II, who also spoke about the clinical equipoise regarding the CV safety of sulfonylurea (SU) drugs, to which pioglitazone was compared in this trial. The need for head-to-head studies in diabetes (as opposed to comparisons to placebo) was emphasized—so the effects of actual treatment options on important patient outcomes can be compared.

The study design was next described by Professor Olga Vaccaro of the same institution. The major goal of TOSCA-IT was to compare the effects of pioglitazone vs. SUs on a composite primary CV outcome of all-cause death, non-fatal MI (including silent MI), non-fatal stroke, and urgent coronary revascularization. The key secondary composite outcome was that of sudden death, fatal and non-fatal MI or stroke, above the ankle leg amputation, and coronary, leg, or carotid arteries revascularization. The trial had a pragmatic design with neither investigators nor patients blinded to treatment (although adjudicators and safety committees, of course, were). The population studied included individuals with Type 2 diabetes, aged 50-75 years, and BMI 20-45 kg/m^2, with suboptimal glycemic control (HbA1c 7-9%) on maximal metformin monotherapy. Exclusion criteria were serum creatinine ≥1.5 mg/dl, heart failure, CV event within 6 months of randomization, and severe liver disease.

Patients were randomized to 15-45 mg of pioglitazone or one of three SUs (gliclazide, glimepiride, or glibenclamide), the specific drug and dose being left to investigators. HbA1c and other CV risk factors were to be treated according to the local standard. If the patient had a persistent HbA1c of ≥8%, basal insulin would be started as 'rescue' therapy. 4956 patients were screened,

3041 randomized, and 3028 analyzed. The treatment duration was long for a CV outcome trial at 57 months. It was anticipated that the trial would run until 498 primary events were tabulated.

At baseline, the groups were equally matched (Table 4) with a mean age in the entire cohort being 62.3 years, 58.6% male, and a mean BMI of 30.3 kg/m^2, HbA1c 7.7%, LDL-cholesterol (C) 103 mg/dl, HDL-C 46.4 mg/dl, and triglycerides 153 mg/dl. 22% had microalbuminuria, 70% were using antihypertensive drugs, 57% were on lipid-lowering agents (mainly statins), and 40% were taking antiplatelet agents. Importantly, only 11% had known CVD, in contrast to the 100% prevalence in both PROactive and IRIS.

Dr. Stefano del Prato next reviewed the glycemic and metabolic outcomes in TOSCA-IT. All patients continued on metformin with a mean daily dose of 2000 mg. In the SU arm, about half the patients were prescribed gliclazide (not available in the US) and half glimepiride, with very few on glibenclamide (which is similar to glyburide in the US). In the pioglitazone arm, the mean daily dose was relatively low at 23 mg.

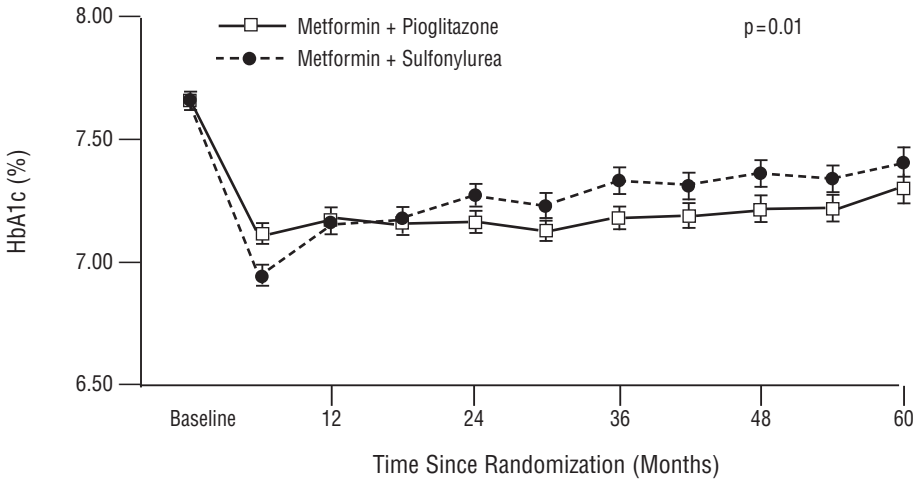
There was a small but significant advantage in terms of glucose lowering to pioglitazone, with a mean HbA1c during the study of 7.24±0.2% vs. 7.30±0.2 % with SUs (p=0.01; Figure 6). Perhaps more impressively, fewer patients on the TZD required rescue insulin therapy during the study (10.7% vs. 15.6%; HR 0.63 [95% CI: 0.52-0.75]; p<0.001). There was also substantially less overall hypoglycemia (glucose <60 mg/dl; 9.6% vs. 32.4%; incidence rate ratio [IRR] 0.27) and less severe hypoglycemia (needing assistance from another; 0.1% vs. 1.6%; IRR 0.06).

During the trial, there were no substantial differences in weight, each group adding about 1 kg. Blood pressure was the same between the two groups, as was LDL-C, triglycerides, and C-reactive protein. HDL-C was slightly higher over time in the pioglitazone group.

Table 4. Baseline Characteristics: TOSCA-IT

	Pioglitazone + Metformin n=1535	*Sulfonylurea + Metformin n=1493*
Age (yrs), mean (SD)	62.3 (6.5)	62.2 (6.5)
Male sex, n (%)	909 (59.2)	865 (57.9)
BMI (kg/m^2), mean (SD)	30.2 (4.4)	30.4 (4.5)
Duration of diabetes in years, mean (SD)	8.4 (5.6)	8.5 (5.8)
HbA1c (%)	7.7 (0.5)	7.7 (0.5)
Cardiovascular Risk Factors		
Smokers, n (%)	281 (18.3)	252 (16.9)
LDL-C (mg/dl)	103.4 (31.7)	102.7 (31.3)
HDL-C (mg/dl))	46.3 (12.1)	46.4 (12.0)
Triglycerides (mg/dl)	152.5 (87.7)	153.4 (82.5)
Systolic blood pressure (mmHg)	134.3 (15.1)	133.7 (14.2)
Diastolic blood pressure (mmHg)	79.5 (8.7)	79.7 (8.1)
Microalbuminuria, n (%)	321 (22.1)	312 (21.9)
Prior Cardiovascular History, n (%)		
Cardiovascular disease	187 (12.2)	148 (9.9)
Myocardial infarction	109 (7.1)	86 (5.8)
Stroke	28 (1.8)	13 (0.9)
Acute coronary syndrome	39 (2.5)	40 (2.7)
Coronary revascularization	105 (6.8)	101 (6.8)
Extra-coronary revascularization	14 (0.9)	12 (0.8)
Cardiovascular Drug Use, n (%)		
Antihypertensive agent	1072 (69.8)	1049 (70.3)
Lipid-lowering drugs	888 (57.9)	847 (56.7)
Antiplatelet drugs	644 (42.1)	574 (38.4)

Figure 6. Glycemic Control Over Time, Pioglitazone vs. SU: TOSCA-IT



Dr. Antonio Nicolucci, from the Center for Outcomes Research and Clinical Epidemiology in Pescara, revealed the main CV outcomes. Ultimately only 213 events actually occurred, and for this reason the trial's Data Monitoring Committee terminated TOSCA-IT due to futility. Moreover, 9.6% and 7.5% of randomized patients in the pioglitazone and SU arms terminated their participation and therefore could not contribute full information to the trial. In addition, 28.1% and 15.9%, respectively, discontinued study drug early, mainly because of adverse effects or concerns about bladder cancer in the pioglitazone group. (This controversy actually emerged half-way through the trial with two nearby countries, Germany and France, withdrawing the drug from their markets. The ensuing 'media storm' likely led many patients to reconsider their full participation). So, the low event rate and a greater number of patients off study drug in the pioglitazone arm eroded into the study's power to detect a difference.

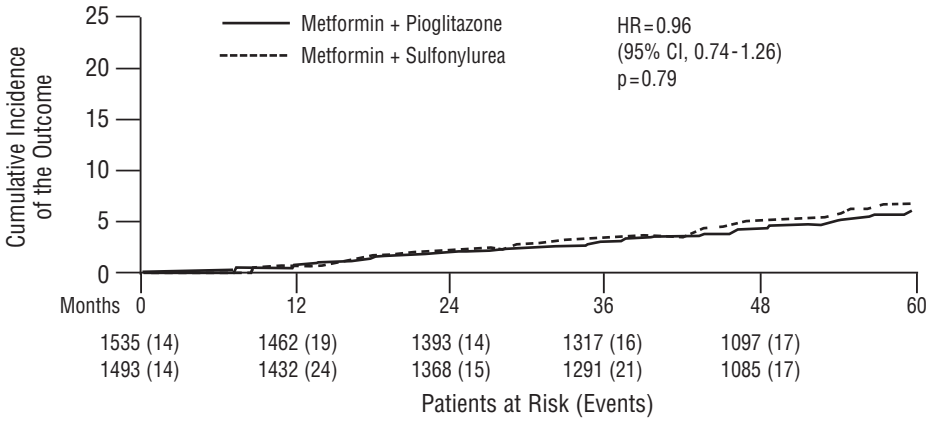
With that caveat, the primary CV composite outcome occurred in 105 patients (6.8%, 1.47/100 patient-years [PYs]) in the pioglitazone group and 108 patients (7.2%, 1.64/100 PYs) in the SU group (Figure 7). The hazard ratio was therefore neutral for pioglitazone (HR=0.96 [95% CI: 0.74-1.26, p=0.79]) vs. SUs. Individual components of the primary outcome were also not significantly different between the groups. The key secondary composite outcome (which included peripheral vascular events) occurred in 74 patients (4.8%, 1.22/100 PYs) in the pioglitazone group and in 83 patients (5.6%, 1.44/100 PYs) in the SU group, for a HR of 0.88 (0.65-1.21, p=0.22).

In an *a posteriori* analysis focusing only on those patients actually still on study drug ('per-protocol' analysis), the primary and secondary outcome HRs were 0.82 (0.60-1.10, p=0.19) and 0.67 (0.47-0.96; p=0.03). So, in those still taking study drug there appeared to be a large benefit on the overall macrovascular event rate, but of only borderline significance—and the p-value was not adjusted for multiple endpoints analyzed.

Dr. Aldo Maggioni from the ANMCO Research Center, Florence presented the safety data. Essentially, aside from the previously presented hypoglycemia data, there were no major differences between the two groups, with all adverse events and serious adverse events equivalent between the two randomized arms. Heart failure occurred numerically more frequently with pioglitazone: 19 (1.2%) vs. 12 patients (0.8%) (HR=1.57 [95% CI: 0.76-3.24], p=0.11]). Cancer rates including bladder cancer (8 in each group) were almost exactly the same, as were fractures and episodes of macular edema.

Professor Enzo Bonora from the University of Verona presented the "Implications for Clinical Practice". He emphasized the demonstrated safety aspects to pioglitazone in TOSCA-IT as a well-tolerated second-line agent after metformin, as is mentioned in the prevailing clinical guidelines from the ADA and EASD. He commented specifically on the issues of fracture and bladder cancer, concerns for which have led to a significant decline in the popularity of pioglitazone. Dr. Bonora also noted the mild glycemic benefit and the strong indication of greater durability in terms of decreased need for insulin injections, as well as the suggestion of a CV benefit in those that adhered to therapy. Finally, hypoglycemia was nearly nonexistent. These points were also reiterated by Professor Marge-Riita Taskinen of the University of Helsinki, who provided independent commentary. She congratulated the TOSCA-IT investigators for a well-done study, particularly considering the controversies about pioglitazone that emerged during its conduct. Her overall conclusion was that pioglitazone should remain a solid and low-cost treatment option in patients with Type 2 diabetes, while acknowledging the trial's overall neutral outcome on CV events.

Figure 7. Time to Primary Endpoint: TOSCA-IT



Primary Endpoint = all-cause death, non-fatal MI (including silent MI), non-fatal stroke, and urgent coronary revascularization

We note that these data are discordant with those from PROactive and IRIS, and suggest the TZD's CV protective effects are only manifested in those with established CVD—i.e., not for primary prevention, at least during the course of a 4 to 5 year clinical trial. Interestingly, subgroup analyses from LEADER, SUSTAIN-6, and CANVAS involving two other classes of glucose-lowering drugs with recently demonstrated beneficial CV effects (GLP-1 receptor agonists [RA] and SGLT-2 inhibitors) had similar results—no clear benefit in primary prevention. Whether more prolonged treatment in those patients without CVD will eventually pay off with a reduction in future events is unknown.

TOSCA-IT had several methodological limitations, including ultimately being underpowered. Also, it was unblinded and had a larger than usual drop-out rate, and an even larger percentage of patients off study drug. Accordingly, the results of this trial must be interpreted cautiously. We continue to feel that this cost-effective generic medication still has a role to play in the therapeutic armamentarium for Type 2 diabetes, where multiple agents used in combination are often required. The recently disclosed benefits of pioglitazone against NASH/NAFLD (Cusi *et al. Ann Intern Med* 2016; 165:305-15) further underscore its utility in other subgroups of patients beyond those with macrovascular disease. Of course, the drug should not be used in those with heart failure and perhaps not in those with osteoporosis, and patients need to be informed about its side effects of edema and weight gain.

Update on Incretin-Based Therapy

Incretin-enhancing drugs, the glucagon-like peptide 1 (GLP-1) RAs and the dipeptidyl peptidase 4 (DPP-4) inhibitors, have now been available for more than a decade. During that time, data have continued to accumulate regarding their efficacy and safety in various patient populations, development of newer agents, and the role of the drugs in combination therapy.

Several sessions at the EASD in Lisbon focused on once-weekly dosed GLP-1 RAs. In a Phase 3 study, Tuttle and colleagues from the US, Brazil, and South Africa randomized (1:1:1) 576 patients with Type 2 diabetes and moderate to severe (stages 3-4) CKD to once-weekly dulaglutide at a dose of 1.5 mg or 0.75 mg or titrated insulin glargine, each group combined with the prandial insulin, lispro (abstract 2). The primary endpoint—change in HbA1c at 26 and 52 weeks from baseline—was comparable in each group, with dulaglutide deemed non-inferior to insulin glargine. Other measures such as body

weight (-3 kg and -2 kg with 1.5 and 0.75 mg dulaglutide, respectively, vs. +2 kg with glargine) and hypoglycemia (glucose ≤70 mg/dl) event rates favored dulaglutide at both time points. Hypoglycemia occurred at a rate of 5.5, 7.8, and 17.1 events/patient/year for dulaglutide 1.5 mg ($p<0.001$), 0.75 mg ($p<0.001$) versus glargine, respectively, at 26 weeks. At 52 weeks, rates were 5.8 with dulaglutide 1.5 mg ($p<0.001$), 7.8 with dulaglutide 0.75 mg ($p=0.004$), versus 14.4 for insulin glargine. Rates of severe hypoglycemia also were more common in the insulin group, whereas, those receiving dulaglutide more often experienced gastrointestinal (GI) side effects of nausea, vomiting, and diarrhea. Overall, dulaglutide was non-inferior to insulin glargine with respect to improvement in HbA1c, with less hypoglycemia and weight gain in patients with Type 2 diabetes and CKD stage 3-4, but at the expense of more GI adverse effects.

Given the weekly administration schedule of dulaglutide, US and Singapore investigators (Patel, *et al*) assessed its glycemic effect over a 7-day dosing interval (abstract 824). A *post-hoc* analysis of data from the AWARD-3 trial (the only monotherapy dulaglutide study) was used to analyze self-monitored blood glucose (SMBG) values segregated by days 1-7 of the dosing schedule after 2-4 weeks, i.e. after steady state had been achieved. Peak values were defined at days 2-3 and troughs at days 6-7. At a dulaglutide dose of 1.5 mg, the mean SMBG (mg/dl) values were 142.2±36 during peak days and 149.4±34.3 during trough days. At the dulaglutide 0.75 mg dose, mean peak and mean trough SMBG values were 140.4±37.8 and 140.4±32.4, respectively. Equivalence between each peak and trough value was based on the 90% CI being contained within ±10% of lower mean peak/trough SMBG. Based on this analysis, the investigators concluded that dulaglutide has a steady impact on blood glucose levels throughout its 7-day dosing interval.

Investigational GLP-1 RA with CV Benefits

Semaglutide,* an investigational once-weekly, GLP-1 RA has been compared to multiple therapies in the SUSTAIN 1-5 clinical trials program in patients with Type 2 diabetes. SUSTAIN-6 was a CV outcomes trial evaluating semaglutide versus placebo with the primary endpoint of composite first occurrence of CV death, non-fatal MI, or nonfatal stroke in patients with Type 2 diabetes at high CV risk. This study demonstrated a previously reported 26% relative risk reduction in CV events, the second member of the class, after liraglutide, to do so. Consoli and co-researchers from Europe and the US reported on a secondary endpoint from SUSTAIN-6: changes in body weight over two years (abstract 4). In this trial of 3,297 patients with baseline mean body weight of 92.1 kg, semaglutide-treated patients demonstrated significant weight loss that persisted at the 2-year mark (mean change of -3.6 and -4.9 kg for the 0.5 and 1.0 mg groups, respectively, vs. -0.5 to -0.7 kg for placebo), along with sustained reductions in BMI and waist circumference (Table 5).

Table 5. Body Weight-related Endpoints: Change from Baseline at Week 104 of SUSTAIN-6

	Overall Mean at Baseline	*Semaglutide 0.5 mg*	*Semaglutide 1.0 mg*	*Placebo 0.5 mg*	*Placebo 1.0 mg*
Number of randomized patients		826	822	824	825
Body weight, kg	92.1	-3.6	-4.9	-0.7	-0.5
ETD vs. placebo	–	-2.87*	-4.35*		
(95% CI)		(-3.47; -2.28)	(-4.94; -3.75)		
Body mass index, kg/m^2†	32.8	-1.3	-1.8	-0.2	-0.2
ETD vs. placebo	–	-1.06*	-1.59*		
(95% CI)		(-1.28; -0.85)	(-1.80; -1.37)		
Waist circumference, cm	110.2	-2.7	-4.2	-0.6	-0.9
ETD vs. placebo	_	-2.17*	-3.25*		
(95% CI)		(-2.82; -1.53)	(-3.89; -2.60)		
Weight loss category, n (%)					
≥5%		297 (36)*	383 (47)*	144 (18)	154 (19)
≥10%		109 (13)*	168 (20)*	47 (6)	54 (7)

*$p<0.0001$. † *Post-hoc* defined endpoint. ETD=estimated treatment difference.

In a related analysis, Lingvay along with North American and European colleagues, evaluated body weight reduction in semaglutide-treated patients versus comparators based on data from SUSTAIN 1-5 (abstract 817). Comparators include placebo (treatment naïve; n=388; SUSTAIN-1); sitagliptin + metformin ± thiazolidinedione (n=1231; SUSTAIN-2); exenatide extended-release (ER) + 1 or 2 oral agents (n=813; SUSTAIN-3); insulin glargine + metformin ± sulfonylurea (insulin naïve, n=1089; SUSTAIN-4); or placebo + basal insulin ± metformin (n=397; SUSTAIN-5). Overall, mean body weight was significantly reduced from baseline with semaglutide (by 3.5 to 6.4 kg) versus all comparators (-1.9 to +1.2 kg) ($p<0.05$ for all). A greater proportion of patients receiving semaglutide achieved ≥5% and ≥10% body weight loss from baseline (all $p<0.05$). Similarly, waist circumference and BMI had the same trends versus each comparator ($p<0.05$ for all). As one might anticipate, the greatest estimated treatment difference for all measures was seen in SUSTAIN-4 (versus insulin glargine). From this analysis, it was determined that semaglutide consistently provides significant reductions in body weight, BMI, and waist circumference in a broad range of patients receiving a variety of therapies for Type 2 diabetes. We would comment that the changes are among the highest we've seen in GLP-1 RA trials.

The previously described SUSTAIN 1-5 trials were also utilized to assess the impact on HbA1c and body weight across HbA1c subgroups (<7.5; >7.5-8.0; >8.0-8.5; >8.5-9.0; and >9.0) by Bain and international colleagues (abstract 813). Semaglutide demonstrated greater efficacy in HbA1c lowering and body weight reduction across all HbA1c subgroups. The greatest reductions in HbA1c were observed in those with higher baseline HbA1c values (as has been the trend in virtually all glucose-lowering drug trials). In contrast, the magnitude of weight reduction was *not* associated with baseline HbA1c. As with all GLP-1 RAs, GI symptoms are more commonly reported than with other glucose-lowering drugs.

GLP-1 RA + Insulin

Another role for the GLP-1 RA is an alternative option for intensification therapy in patients inadequately managed with basal insulin. Intensification with insulin is often undesirable due to fear of hypoglycemia and weight gain, and typically requires more frequent injections at mealtimes (basal-bolus therapy). International investigators, Jodar *et al.* used patient-reported outcomes (PROs) to assess perceived health status and treatment experiences when the combination of liraglutide and degludec (IDegLira) was compared with traditional basal-bolus therapy in

Type 2 diabetes patients (abstract 804). In an open-label trial, patients with baseline HbA1c values of 7-10% on metformin and insulin glargine (20-50 units daily) were randomized (1:1) to receive either once daily IDegLira, a premixed fixed formulation of the basal insulin plus the GLP-1 RA, or basal bolus insulin (once-daily glargine U100 plus insulin aspart ≤4 times daily). Various PRO questionnaires (e.g., Short Form Health Survey 36 v2 [SF-36] and Treatment-Related Impact Measure-Diabetes [TRIM-D]) were utilized to assess potential differences between the groups. Each group achieved similar glycemic control at 26-weeks, but IDegLira resulted in greater improvements in PROs (Table 6), including willingness to stay on combination therapy (84.5% versus 68.1%; OR 2.54 [95% CI 1.63; 3.98], p<0.001) and others.

Table 6. Change from Baseline to Week 26 in TRIM-D Domain Scores

	IDegLira + Met Observed Mean Change (n=252)	*IGlar U100 + IAsp + Met Observed Mean Change (n=254)*	*Estimated Treatment Difference (95% CI)*	*p-value*
Diabetes management	16.7	6.8	10.76 (7.62; 13.90)	<0.0001
Treatment burden	12.4	4.3	10.50 (7.34; 13.67)	<0.0001
Compliance	9.1	3.9	6.25 (3.82; 8.69)	<0.0001
Daily life	3.5	-0.4	4.23 (1.09; 7.37)	<0.0083
Psychological health	5.7	3.0	2.77 (0.32; 5.21)	0.0268

CI=confidence interval; IAsp=insulin aspart; IDegLira=insulin degludec/liraglutide; IGlar U100=insulin glargine 100 units/mL; Met=metformin; MMRM=mixed-model repeat measurement; TRIM-D=Treatment-Related Impact Measure-Diabetes.

Note: Positive number denotes improvement in parameter being measured.

An Oral GLP-1 RA?

While weekly (versus once or twice daily) injections of GLP-1 RAs likely improve patient satisfaction with this class of agents, oral therapy would be even more desirable. The investigational oral, non-peptide GLP-1 RA, TTP273,* was evaluated in a Phase 2 study by Freeman and US co-researchers (abstract 112). Safety and efficacy were assessed in a 12-week, double-blind, placebo-controlled trial in patients with Type 2 diabetes (n=174) on stable doses of metformin. Primary endpoint measures included: HbA1c, weight, and GI tolerability. TTP273 at doses of 150 mg po nightly or 150 mg po twice daily were compared with placebo. Placebo-subtracted decreases from baseline in HbA1c were 0.9±0.2% for once-daily dosed and 0.7±0.2% for twice-daily dosed study drug, both p<0.001. Placebo-subtracted weight loss was 0.9±0.5 kg for once daily (p=0.08) and 0.6±0.5 kg for twice daily. Interestingly, lower daily doses of TTP273 demonstrated greater response rates relative to HbA1c and body weight, with greatest reductions achieved at doses <1.35 mg/kg. TTP273 was generally well tolerated. Diarrhea occurred in 2%, 3%, and 12% of patients receiving placebo, once-daily, and twice-daily; lower rates of nausea were reported in the treatment arms, and vomiting occurred in one patient in the placebo arm. No severe hypoglycemia occurred in any patient. In this preliminary analysis, the investigators suggested that oral GLP-1 RAs can be efficacious without eliciting nausea and vomiting commonly observed with injectable formulations. Clearly, additional investigation is required, focusing on optimal dosing as well as confirmation of lower incidences of nausea and vomiting and the potential mechanism(s) underlying this. And, of course, this agent, if development continues as planned, will need to be studied for CV safety and effectiveness.

New Data on DPP-4 inhibitors

One of the advantages of the incretin enhancers is their relative lack of hypoglycemia. However, it remains a concern when these therapies are added to insulin, particularly in the elderly, who may be more hypoglycemia prone and at greater risk of harm when hypoglycemia occurs. Shankar and US co-investigators assessed the impact of the oral DPP-4 inhibitor, sitagliptin, when added to insulin in elderly (≥65 years) Type 2 diabetes patients (abstract 781). Data from two 24-week studies comparing addition of sitagliptin versus placebo to insulin (± metformin) was analyzed by age (< 65 years and ≥ 65 years) in a pooled analysis assessing glycemic control and hypoglycemia event rates. HbA1c reductions were similar in both age groups for sitagliptin (~ -0.9 to -1.0%) and in both age groups for placebo (-0.4 to -0.5%). Event rates for hypoglycemia were comparable or lower in the elderly (versus younger) groups, regardless of drug; yet symptomatic and nocturnal event rates for hypoglycemia were lower, but not statistically significant, for either age in sitagliptin treatment arms (1.32 symptomatic events/year with sitagliptin versus 2.18 events/year with placebo in the <65-year age group; and 1.50 versus 1.65 in the elderly). Nocturnal events/patient year were 0.66 in the sitagliptin arm versus 0.89 with placebo for younger subjects (ns) and 0.38 with sitagliptin and 0.90 with placebo in elderly subjects (p<0.05). The overall conclusions from this pooled analysis are that when sitagliptin is added to insulin, there are improvements in glycemic control with actual reductions in hypoglycemia in both younger and older patients. The mechanisms by which this drug can reduce glucose without increasing hypoglycemia is not well understood but might involve better glucagon signaling. Similar reports emerged several years ago with another DPP-4 inhibitor, linagliptin (Inzucchi *et al. Diabetes Obes Metab* 2015).

Acarbose: No Aces in ACE

In the Roma Hall at the Feira Internacional de Lisboa on Wednesday, the ACE investigators presented their long-awaited trial results. ACE stands for "Acarbose Cardiovascular Evaluation", a recently completed randomized, double-blind clinical trial of the alpha-glucosidase inhibitor (AGI), acarbose, versus placebo in 6522 Chinese patients with impaired glucose tolerance (IGT) and prevalent coronary heart disease. Interestingly, 9.7% of the adult population in China currently has diabetes, totaling 100 million individuals and about half the population (about 500 million) can be categorized as having prediabetes (either by IGT, high fasting glucose, or HbA1c). So diabetes prevention strategies are urgently needed.

However, ACE, while it did track the conversion of IGT to diabetes, was primarily a CV trial.

Although rarely used in the US, the AGIs still have a substantial presence in East Asia as glucose-lowering drugs for Type 2 diabetes. They are relatively modest in efficacy, lowering HbA1c only about 0.5% on average. AGIs block carbohydrate absorption in the small bowel and thereby target post-prandial glucose excursions. Their main side effect is abdominal gas.

In the only large prior placebo-controlled acarbose trial, STOP-NIDDM (Chiasson *et al. Lancet* 2002), the drug was found to prevent (or delay) the risk of developing diabetes in 714 patients with IGT by 25%. In a post-hoc analysis from that study, CV events appeared to be reduced by 49% in the acarbose arm, driven mainly by a 91% reduction in the risk of MI.* Frankly, few of us gave much credence to those CV results because it was difficult to imagine how such a weak glucose-lowering drug without any other substantive effects on CV risk factors could possibly have such an effect. The drug class never achieved any significant market share in the US or in much of Europe, and has therefore not been included in most treatment algorithms in Western countries, including that from ADA-EASD.

In the ACE population, the mean age was about 64 years, and 27% were female. The mean BMI was 25.4 kg/m^2, HbA1c 5.9%, FPG 99 mg/dl, and 2-hour postprandial glucose (2-hr PG) during the baseline oral glucose tolerance test (OGTT) 167 mg/dl. 41% had had a prior MI, 42% previous unstable angina, and 22% current chronic stable angina. The participants exhibited extensive use of background evidence-based CV medications; e.g., 93% were taking statins and 94% were on aspirin.

Metabolic changes were very modest during the trial, likely reflecting the relatively low dose of acarbose that was chosen (50 mg TID). HbA1c was 0.07% better in the active treatment arm and 2-hr OGTT PG was reduced by 24 mg/dl. Except for more GI adverse effects in the acarbose group, the safety profile was equivalent to placebo.

The study's primary outcome was a 5-point CV composite consisting of CV death, non-fatal MI, or stroke, and hospitalization for unstable angina or heart failure. The key secondary outcome was classical 3-point MACE (CV death, non-fatal MI or stroke.) Neither was appreciably affected by the study drug. The respective HRs (95% CIs) were 0.98 (0.86-1.11; p=0.73) and 0.95 (0.81-1.11; p= 0.51)—essentially a neutral effect.

The only positive outcome was an 18% relative risk reduction for developing diabetes (HR 0.82 [0.71-0.94; p=0.005])*—similar to the effect in STOP-NIDDM.

It was concluded that this AGI has no substantial CV benefit when used in an IGT population with established CVD but did have a modest effect on preventing (or delaying) Type 2 diabetes. We don't think the ACE results will rejuvenate any interest in this drug class. We also feel that this trial's results may finally put to rest the controversy as to whether post-prandial glucose should be specifically targeted in order to reduce CV complications of diabetes. This notion has been in the diabetes community for decades—but never confirmed.

Low-Down on Hypoglycemia

Hypoglycemia has always been the treatment-limiting event in the management of diabetes. Fortunately, our ability to more accurately detect it is developing rapidly with new technologies. Several presentations at this year's EASD focused on hypoglycemia and its complications.

Brian Frier MD from the University of Edinburgh, UK clarified some misperceptions about hypoglycemia as well as giving credence to the concern that hypoglycemia is associated with as many complications as hyperglycemia. It is generally known that both mild and severe hypoglycemia events are 3-fold more frequent in people with Type 1 than Type 2 diabetes (Donnelly *et al. Diabetic Med* 2005). It is less known that the incidence of mild hypoglycemia remains relatively constant over time, while the incidence of severe hypoglycemia increases with longer duration of disease (Pederson-Byergard *et al., DMRR* 2004:20: 479-86). Increasing risk of severe hypoglycemia is likely a result of impaired counter-regulation that occurs over time, including an initial decrease in glucagon response by 5 years, followed by impaired adrenaline response after about another 10 years. With this comes an impaired awareness of hypoglycemia (IAH), which is defined as diminished ability to perceive the onset of acute hypoglycemia. Importantly, Dr. Frier emphasized that IAH is not associated with autonomic dysfunction, which is a common misperception. One of the most effective screens to identify people with IAH is the Hypoglycemia Awareness Questionnaire involving 33 questions and takes 7 minutes to complete (Speight *et al., Diabetes Med* 2016;33:376-85).

In a related presentation, Sepulveda and colleagues from Portugal and the UK presented data from multiple separate questionnaires assessing the presence of IAH and cognitive abilities in 85 adults with Type 1 diabetes (abstract 722). This cohort was 38.4±12.5 years of age with diabetes duration of 19.1±11.7 years, and 16.5% had IAH by the older Clark score. Those with IAH had significantly lower executive functioning performance (p<0.05), more neuroglycopenic symptoms when hypoglycemic (p=0.03), more barriers to activity (p=0.01), and more depression (p<0.01) than those with preserved hypoglycemia awareness. People with severe hypoglycemia in the past year had worse language performance (p=0.02), more neuroglycopenic symptoms (p=0.003), and higher depression scores (p=0.04) than people without severe hypoglycemia.

Dr. Frier spoke candidly about the difficulties in managing people with IAH, emphasizing that many individuals do not alter their behavior to prevent, avoid, or correct hypoglycemia, in addition to being less adherent to recommended changes in insulin management. In support of this, Cook and colleagues from the UK, US, and Australia analyzed responses to the Attitudes to Awareness Questionnaire in a cross sectional survey of 1978 Americans with Type 1 diabetes (abstract 723). The cohort characteristics included a mean age of 40±16 years, 62% female, disease duration of 23±14 years, and HbA1c 7.8±1.4%. IAH was present in 37% of the cohort, and recurrent symptomatic hypoglycemia was present in 14%. The three most important behavioral factors to explain the occurrence of hypoglycemia in this cohort included: 1) minimizing concern about the negative effects of hypoglycemia, 2) excessive prioritization on avoiding high blood glucose, and 3) lack of concern about asymptomatic hypoglycemia. Those with IAH prioritized avoiding hyperglycemia more than people without IAH (p=0.003), but were less likely to minimize concern about hypoglycemia (p=0.001). Patients with recurrent symptomatic hypoglycemia were more likely to normalize

asymptomatic hypoglycemia than those without recurrent symptomatic events (p=0.002).

Newer data on the consequences of hypoglycemia are promoting a paradigm shift in thinking about its risks, especially with regard to CV consequences. Hypoglycemia quickly affects microvascular flow and function, autonomic output and hormone secretion, as well as coagulation parameters. These physiological sequelae may last for up to a week.

Patients with severe hypoglycemia were twice as likely than those without events to experience major adverse CV events, CV death, and all-cause death (all, p<0.0001), in a sub-analysis of the LEADER trial (abstract 158). LEADER was a CV outcomes trial which showed liraglutide decreased the risk of CV events as well as hypoglycemia, relative to placebo, when added to standard-of-care in 9,340 people with Type 2 diabetes. Standard-of-care more frequently involved SUs and/or insulin. Of these, 267 people experienced severe hypoglycemia, and the CV event rate or death was considerably higher in the 60 days following the episode.

With further concerns for hypoglycemia related mortality, Teh and colleagues from Singapore reported that 22.5% of people admitted to hospital with severe hypoglycemia died within one year of admission (abstract 730). The cohort who died were older (mean age 75±11 vs. 69±11 years, p<0.05), had more co-morbidities (p<0.05) and longer hospital stays (10 vs. 5 days, p<0.05) than the cohort who survived the year following hypoglycemia admission. Interestingly, the degree of glycemic control did not influence the 1-year mortality rate, but overall the groups had well-controlled diabetes (HbA1c 6.9±1.4%).

In summary, there is accumulating evidence that hypoglycemia events are not just an inconvenience and limiting factor to tight glycemic control. With risk for CV events and longer-term cognitive dysfunction, identifying hypoglycemia by more intensive monitoring, specifically continuous glucose monitoring, may become a more commonly used modality in diabetes care, especially in Type 1 diabetes. Other technological advances that are helping to prevent hypoglycemia include insulin analogues and insulin pumps.

So Many Posters, So Little Time....

Cup 'o Joe?

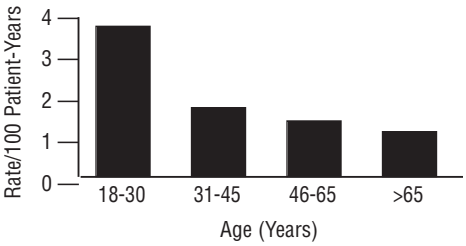
Neves and Portugese investigators examined the association of caffeine consumption with mortality among patients with diabetes using data from National Health and Nutrition Examination Survey (NHANES), 1999-2010 (abstract 841). Caffeine consumption was assessed at baseline using 24-hour dietary recall. Cox proportional hazard models were fitted to estimate hazard ratios for all-cause, CV, and cancer-related mortality according to caffeine consumption and its source (coffee, tea, or soft drinks). The data were adjusted for potential confounders (age, race, education level, annual family income, smoking status, BMI, daily carbohydrate consumption, alcohol consumption, years since diabetes diagnosis, hypertension, diabetic kidney disease, retinopathy, macrovascular complications, and insulin treatment).

A dose-dependent protective effect of caffeine consumption on all-cause mortality was observed among women with diabetes (0.49 [95% CI: 0.33-0.74] for <100 mg/day [95-165 mg caffeine per 8 ounce cup of coffee], 0.43 [0.26-0.70] for 100 to <200 mg/day, 0.34 [0.20-0.57] for ≥200 mg/day; p=0.007), but not men with diabetes. Among women with diabetes, the effect on mortality depended on the source of caffeine, with a protective effect of coffee consumption on all-cause death (p=0.007) and CV death (p=0.041), and a protective effect of caffeine from tea on cancer deaths (p=0.009). The reasons for these associations are unknown but could also be explained by unmeasured confounders.

Epidemiology of DKA

Using data from a health registry of 491,654 patients with diabetes in Austria and Germany, Schmid and coworkers reported on event rates and risk factors for DKA in 48,067 adults with Type 1 diabetes (52.3% male, median age 38.6 years, median duration of diabetes 13.6 years) (abstract 334). For the most recent year of observation in each patient, the DKA event rate (analyzed based on a Poisson regression model) was 2.54 hospital admissions per 100 patient years (95% CI: 2.10-3.05). The event rate was highest in the youngest adults (adjusted p<0.0001 vs. older patients; Figure 8), with no difference by gender. Insulin pump therapy was not associated with a higher rate of DKA (2.43/100 patient-years) compared to multiple daily insulin injections (2.83/100 patient-years; p=0.11).

Figure 8. Rate of Diabetic Ketoacidosis in Patients with Type 1 Diabetes by Age



Just a Sniff…

Seaquist and North American investigators evaluated nasal glucagon 3 mg for moderate or severe hypoglycemic episodes* in real-world settings in adults with Type 1 diabetes (abstract 739). Glucagon was administered intranasally in less than 30 seconds for most events (70.4%) and less than minutes in nearly all (97.7%). According to questionnaire responses of patients/caregivers, most patients (96.2% of 157 hypoglycemia events) returned to normal status within 30 minutes; patients recovered within 30 to 45 minutes of glucagon administration for 5 of the 6 remaining events. None of the patients required an emergency call.

Mean blood glucose at hypoglycemia event onset was 49 (range 22 to 74) mg/dL and increased to 113 mg/dL (range: 43 to 266) by 30 minutes, increasing progressively thereafter. All 12 severe events (in 7 patients) resolved, with patients awakening or returning to normal status within 15 minutes.

Most patients experienced nasal irritation (82.4%). The majority (82.7%) of caregivers were satisfied or very satisfied with the process after most hypoglycemia events. These findings suggest that nasal glucagon is a potential alternative to currently available injectable glucagon as treatment for severe hypoglycemia.

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

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Diabetes2017

From the 53rd Annual Meeting of the European Association for the Study of Diabetes ■ Lisbon, Portugal

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Happy Birthday, Metformin!

This year marks the 60th anniversary of the discovery of the biguanide metformin, a landmark acknowledged by a special edition of *Diabetologia*, the flagship journal of the EASD—copies of which were distributed to all attendees this week. Despite many decades of use, we are still learning more about this safe, inexpensive, and highly effective glucose-lowering agent, still considered 'first-line' in the management of patients with Type 2 diabetes by most practitioners.

Dr. Gerald Shulman, Yale University School of Medicine, New Haven, CT, ("Will We Ever Understand Metformin?") discussed the complexities of metformin's mode of action during a symposium to mark this anniversary.

Metformin is one of the most effective options for treating Type 2 diabetes because it reduces hepatic glucose production (primarily gluconeogenesis) without increasing insulin secretion, inducing weight gain, or increasing the risk of hypoglycemia. Despite its long-term and widespread use, the underlying mechanism by which metformin inhibits hepatic gluconeogenesis remains unknown. Initial investigations into metformin action found it to be a mitochondrial complex I inhibitor at millimolar concentrations—typically higher than is achieved in humans. More recent studies suggested that metformin activates AMP-activated protein kinase (AMPK) leading to reduction of gluconeogenic gene transcription. Other lines of evidence indicated that metformin's effect is actually AMPK-independent, inducing allosteric inhibition of glycolytic enzymes. More recently, non-hepatic mechanisms have also been proposed, such as activation of gut incretin factors. Given these conflicting results, it is apparent that the actual mechanisms by which biguanides exert their therapeutic effects remain to be fully explained.

Shulman presented his lab's recent work that shows metformin to be a non-competitive inhibitor of the mitochondrial enzyme glycerol-3-phosphate dehydrogenase (GPD) at clinically relevant concentrations (~50 micromolar). The resulting increase in the cytosolic redox state (and concomitant reduction in the mitochondrial redox state) leads to reduced conversion of lactate and glycerol to glucose and, as a result, decreased gluconeogenesis. In support of this theory, his group has additionally shown that antisense oligonucleotide knockdown of hepatic mitochondrial GPD in rats resulted in a phenotype akin to chronic metformin treatment and also abrogated any further metformin-mediated inhibition of hepatic glucose production. These findings were then replicated in whole-body mitochondrial GPD knockout mice. Taken together, these results have significant implications for understanding the mechanism of metformin's blood glucose-lowering effects. They also provide a new therapeutic target for Type 2 diabetes.

Several abstract presentations this week also delved deeply into the drug's mechanistic properties. It has recently been shown that patients with Type 2 diabetes have an altered bacterial composition in their intestines compared with non-diabetic individuals. Nielsen and Danish colleagues investigated whether adaptations in gut microbiota composition occur in response to metformin treatment, independent of the diabetic state (abstract 241). As we all know, one of metformin's most common side effects is diarrhea. The investigators enrolled 26 young, healthy, lean men in an 18-week study comprised of a 6-week run-in period, a 6-week intervention period with metformin (500 mg daily, increased by 500 mg weekly to a total dosage of 2000 mg daily), and a 6-week wash-out period. Participants were examined 5 times (before and after the run-in period, halfway through and immediately after the intervention, and after the wash-out period) in the fasting state, with blood-sampling and recording of gastrointestinal symptoms. Stools were collected at nine evenly distributed time points, and bacterial DNA was extracted and subjected to 16S-rRNA-sequencing in order to evaluate microbiome composition.

Twenty-three men (mean age 25.7 years, mean BMI 22.9 kg/m^2) completed the intervention. Plasma vitamin B_{12} and HbA1c concentrations declined following intervention ($p=0.01$ and

p=0.03, respectively). The relative abundance of 20 operational taxonomic units (OTUs) changed during the 6-week intervention. Several OTUs of the order Clostridiales were depleted, including one assigned to *Intestinibacter bartlettii* and two *Clostridium* spp. In contrast, *Alistipes finegoldi* of order Bacteroidales and an OTU assigned to genus *Escherichia/Shigella* were enriched. All OTUs recovered to pre-intervention levels within 3-6 weeks of treatment cessation. Changes in gut microbiota composition were accompanied by an increase in self-reported intestinal discomfort. These results substantiate and extend previous cross-sectional findings by this research group, that concluded that additional studies are needed to further examine to what extent metformin exerts its glucose-lowering properties as well as its adverse gastrointestinal effects by modifying gut bacteria.

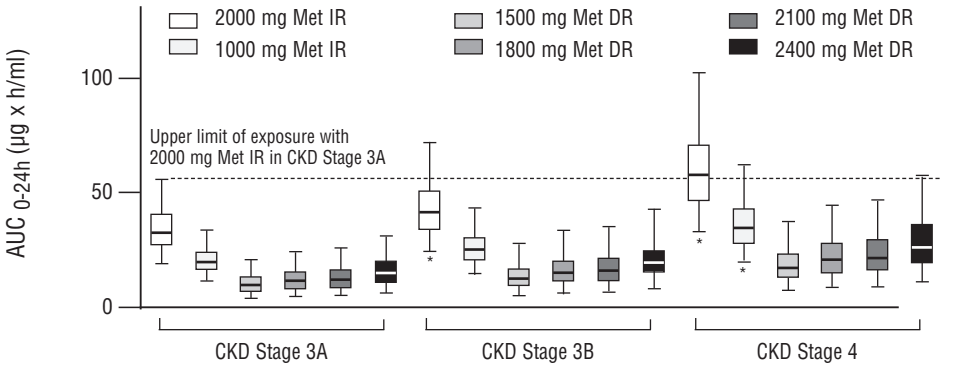
So, it is evident that, after 60 years, we still don't understand fully how metformin actually works! We suspect that multiple mechanisms are at play.

Metformin Safety and Use in CKD

Due to lactic acidosis risk, metformin has always been considered contraindicated in those with renal disease. Last year the US FDA relaxed the prescribing guidelines for this drug. It is now allowed to be used when the eGFR is >30 ml/min/1.73m^2, although only cautiously when the eGFR is <45 ml/min/1.73m^2. Delayed-release metformin (Met DR)* is under development as an ostensibly safer option for Type 2 diabetes patients with CKD (Stage 3B or 4). Enteric coating of Met DR allows the stomach and upper intestine to be bypassed, delivering metformin to the lower bowel and thereby retaining its proposed gut-based glucose-lowering properties (stimulates GLP-1 secretion), but with greatly reduced absorption and systemic exposure. The results of studies by 2 groups of US researchers have further characterized exposure and response following Met DR dosing, as summarized below.

Bakris and US colleagues developed a population-pharmacokinetic model to characterize the absorption and disposition of immediate-release metformin (Met IR), extended-release metformin (Met XR), or Met DR at varying doses in subjects across a range of renal impairment (abstract 244). The model was developed using 5,854 plasma and 762 urine observations from 108 subjects who received orally administered single or multiple doses of Met IR, Met XR, or Met DR in subjects with varying degrees of renal impairment. Each simulation comprised 1000 subjects with varying body weight and renal function. eGFR values were assumed to arise from uniform distributions between 45-59.5 mL/min/1.73 m^2 (CKD Stage 3A), 30-44.5 mL/min/1.73 m^2 (CKD Stage 3B), and 15-29.5 mL/min/1.73 m^2 (CKD Stage 4). Met DR relative bioavailabilities were estimated from noncompartmental analyses of data from two comparative bioavailability studies. Predicted steady-state exposures ($AUC_{0\text{-}24h}$) with Met DR doses of up to 2100 mg were no higher in CKD Stage 4 than those with the FDA-approved 2000 mg dose of Met IR in patients with CKD Stage 3A (Figure 9). These results indicate that metformin exposure with gut-restricted delayed-release metformin in CKD Stage 4 does not exceed that of current metformin "on-label" use. This suggests a favorable benefit/risk profile for patients with CKD Stage 3B currently receiving metformin, or a novel option to initiate metformin for patients with CKD Stage 3B/4.

Figure 9. Metformin Exposure With Metformin DR in Subjects with Varying Degrees of Renal Impairment



In a related study, Fineman and US coworkers randomized 571 patients with Type 2 diabetes and CKD Stage 1 or 2 to 16 weeks of double-blind Met DR (600, 900, 1200, 1500 mg QD) or placebo, or to unblinded 2000 mg Met IR (1000 mg BID; 1000 mg QD for first week) (abstract 243). 542 of them (mean 56 years old, 53% male, 7.9±6.7 years of Type 2 diabetes, BMI 32±5 kg/m^2, HbA1c 8.6±0.9%) were included in the analysis population for exposure, efficacy, and safety analyses.

Metformin plasma exposure (estimated $AUC_{0\text{-}24h}$) with Met DR was ≤37% of Met IR. Met DR resulted in a significant (p<0.05) dose-dependent HbA1c change (1200 mg: -0.49±0.13%; 1500 mg: -0.62±0.12%; PBO: -0.06±0.13%), and Met IR 2000 mg, -1.10±0.13%. Fasting plasma glucose (FPG) improvement was significantly greater with 900-1500 mg Met DR vs. placebo, and approached that of 2000 mg Met IR (-25.1±4.1 vs. -32.6±4.2 mg/dL, respectively). Also, GI adverse events were generally less common with DR (<16% at all doses) than IR (28%). Nausea specifically was a much lower with the investigational formulation (1-3% vs. 10% Met IR), likely due to Met DR's bypassing the stomach. Taken together, 1500 mg Met DR may provide an improved benefit/risk profile in patients for whom minimizing metformin exposure is desirable, such as patients with advanced CKD. Of course, large studies will be necessary to determine safety and efficacy.

Insulin Therapy: What's New?

Plum-Morschel, representing a multi-national group from Germany and Denmark, presented data on a new oral basal insulin known as insulin 338* from a phase 2 double-blind, multiple site trial comparing insulin-338 to the commonly used injectable basal insulin glargine, in 50 insulin-naïve people with Type 2 diabetes already receiving metformin and other oral agents (abstract 74). Insulin-338 has a 70-hour half-life and the advantage of higher liver clearance, similar to endogenous insulin. After 8 weeks, FPG and 10-point glucose profiles were similar between groups. However, the insulin-338 group had a slightly higher mean HbA1c (7.3±0.8 vs. 7.1±0.6%, p=0.077) and greater fasting glycemic variability within each

participant (p=0.078) compared to glargine. These did not reach statistical significance in this small study. Hypoglycemia events were uncommon, with 7 events in 6 insulin-338 treated patients and 11 events in 6 glargine-treated patients. These results are promising for a "starter" insulin in people with Type 2 diabetes, especially since Thorsted and colleagues from the US (abstract 667) found that 81% of Type 2 diabetes patients had ongoing uncontrolled glycemia after 6 months of injectable basal insulin therapy, in a retrospective review of the QuintilesIMS PharMetrics Plus Health Plan Claims database. Clearly, in the real world, there are still many barriers for both patient and practitioner to obtaining glycemic control with insulin.

On the prandial insulin front, several studies examined the efficacy of newer, faster-acting insulins for mealtime use. So-called 'fast-acting insulin aspart'* was compared to traditional insulin aspart, a commonly used mealtime insulin analogue, over two 26-week treatment periods (abstract 688). After 52 weeks, the change in HbA1c from baseline was significantly greater with the faster version (-0.08% vs. +0.01%, p=0.04), which is most likely due to a lowering of 1-hour post-prandial glucose levels (-18.9 vs. -2.5 mg/dl, p=0.0002). No differences in post-prandial glucose were noted at 2, 3, and 4 hours. The investigational ultra-rapid 'BioChaperone lispro'* (BCLIS) was compared directly to conventional lispro (another common mealtime insulin analogue) in a 14-day treatment study in individuals with Type 1 diabetes (abstract 686). BCLIS and lispro were given at the time of the meal. BCLIS also showed a significant decrease in glucose through the first 1 and 2 hours post-meal (glucose area under the curve [AUC] 0-1 hour: 19.7 vs. 32.7 mg x hr/dl, p=0.006; 0-2 hours: 62.1 vs. 90.2 mg x hr/dl, p=0.02). The effectiveness of BCLIS to increase circulating insulin levels faster is seen by a doubling of insulin AUC in the first 30 minutes, relative to lispro (insulin AUC 0-30 minutes: 60 vs. 34 pmol x hr/ml, p<0.0001) By 2-hours, this difference was gone, demonstrating a "faster-in and faster-out" phenomenon to target the fast swing of post-prandial glucose. It remains unclear if these more rapid insulin analogues (which will likely be more expensive) will have any real impact on overall glycemic control, as measured by HbA1c or on hypoglycemia rates. Our colleagues working on so-called 'closed-loop artificial pancreas' systems tell us, however, that they may be key in getting quicker responses from insulin pumps as they react automatically to changes in interstitial glucose concentrations as measured by continuous glucose monitoring (CGM) devices.

Since the advent of new insulin technologies will be applied to the growing number of people with Type 2 diabetes, Owens *et al.* from the UK presented data on how baseline fasting C-peptide may predict efficacy and safety outcomes for insulin therapy (abstract 75). They studied 2165 patients who were to begin glargine therapy, and grouped them based on fasting C-peptide levels: ≤0.4 (4.6%), 0.4-1.2 (58.5%), 1.2-2.0 (28.7%), and >2.0 (8.2%) ng/ml). Of note, baseline BMI was strikingly different between groups (25.7, 29.5, 31.9, and 32.2 kg/m^2, respectively), demonstrating that diminished beta cell function is a more prominent defect in relatively leaner individuals with Type 2 diabetes. While the differences in HbA1c were similar between groups after 24 weeks of titrated glargine therapy, insulin dosing was lower in the cohorts with lower baseline C-peptide—0.34, 0.42, 0.51, and 0.50 U/kg/day, respectively. The most prominent difference was in the number of patients affected by hypoglycemia (<70 mg/dl) that occurred in 66%, 51%, 43%, and 34% of patients respectively, and nocturnal hypoglycemia that occurred in 35%, 22%, 16%, and 11% of patients, respectively. While this study demonstrates a way to categorize the heterogeneous Type 2 diabetes population, it is unclear whether C-peptide levels are more effective than BMI in indicating who will need lower doses of insulin to prevent hypoglycemic events, especially since this by-product of insulin secretion is affected by several factors beyond beta cell function.

For Type 2 diabetes patients with high BMI's, U-500 concentrated insulin is an option to provide higher insulin doses with lower volumes. Deberles and colleagues from France (abstract 680) retrospectively reviewed the effectiveness of switching U-100 rapid-acting insulin to U-500 insulin administered via pump device. They found that pump therapy delivering U-500 durably improves glycemic control in insulin-refractory patients with Type 2 diabetes.

Lipodystrophy due to insulin injections is often overlooked as a cause of uncontrolled glycemia. Risk factors for lipodystrophy development include using the same skin region for injection, long duration of diabetes, and poor education on insulin injection technique. Maksymiuk-Klos and Polish collaborators (abstract 1168) detected lipodystrophy in 51% of 60 patients with Type 1 and 2 diabetes using a thermal imaging camera, as opposed to 15% of patients detected with subcutaneous lesions by palpation. Since this camera is safe, non-invasive, and inexpensive, its use might be considered in specialty clinics with large populations on insulin.

In summary, the field of insulin therapy continues to advance. The most promising developments have been in novel insulin formulations. The goal is to allow for more physiological glucose control, hopefully with less hypoglycemia, and, preferably, more convenient delivery systems. Of course, these advantages must be definitively proven in clinical trials before regulators approve these agents.

We'd like to make one final point, as reviewed in our newsletters from the ADA in San Diego in June (*Diabetes 2017*, Volume 35, Issue 1). The prices of insulin have skyrocketed over the past 5 years and are now difficult to justify. In our practice, patients skipping their insulin or taking it at reduced dosages is not uncommon simply in an effort to save costs. The pharmaceutical industry needs to address this growing crisis urgently so that this life-sustaining drug is made more widely available. Alternatively, clinicians should refamiliarize themselves with the safe use of older and cheaper human insulins (e.g., NPH, Regular), which can be used safely in many patients. (see: Lipska KJ *et al. JAMA* 2017;318:23-24).

Novel Strategies for Obesity

Transcranial Magnetic Stimulation (rTMS), a non-invasive technique that can change neural excitability and dopamine release, has been developed as a treatment for neuropsychiatric disorders associated with abnormal dopamine release. It has been hypothesized that rTMS can induce satiety and weight loss through modulation of food craving circuitries ("food reward system"). Interested in the effects of rTMS on body weight, Luzi and Italian researchers randomized 28 obese patients (20 female, mean age: 46.3±9.4 years, mean BMI 36.6±4.9 kg/m^2) to receive 15 daily sessions of high frequency stimulation to the prefrontal cortex and insula, bilaterally (18 Hz, promoting cortical excitability); low frequency stimulation (1 Hz, inhibiting cortical excitability); or sham stimulation (3 per week for 5 weeks) (abstract 230).

Individuals in the 18 Hz group achieved significant weight loss after the 15 sessions of treatment (-4.1% of body weight, p<0.001 vs. baseline), and at 1 month (-5.5%, p<0.001 vs. baseline) and 6 months of follow-up (-4.8%, p=0.014 vs. baseline). This correlated with a

decrease in food craving at the same timepoints (-42%, -39%, -42%, respectively; each $p<0.0001$ vs. baseline; $p<0.01$ vs. sham at 6 months). Reductions of ACTH (-37%, $p=0.002$ vs. baseline), prolactin (-43%, $p<0.0001$ vs. baseline), TSH (-21%, $p=0.019$ vs. baseline), and norepinephrine level (-11%, $p=0.078$ vs. baseline) were also found at the end of the 15 sessions in the high-frequency group; TSH decrease persisted up to 1 month of follow-up (-19%, $p=0.009$ vs. baseline). In the 18 Hz group, a trend to reduction in the norepinephrine levels (-11%, $p=0.078$ vs. baseline) was observed after 15 rTMS sessions. Conversely, in the low-frequency group, neither significant weight change nor hormone changes were shown. The investigators concluded that high frequency rTMS reduced food craving, leading to significant weight loss for up to 6 months, via modulation of neuroendocrine axes and sympathetic activity.

Ryder and English coworkers established a UK NHS EndoBarrier™ service for patients with suboptimally controlled Type 2 diabetes and obesity (abstract 701). The patients had EndoBarrier™, a 60 cm endoscopically-implanted proximal intestinal liner, inserted for treatment of their obesity and diabetes and received encouragement to effect behavior changes during the period of up to 1 year of the device, which blocks absorption, but may also modulate gut neuroendocrine secretion. Since its inception, 42% (65/153) of referred patients were accepted for treatment, 50 had an Endobarrier™ implanted, and 31 patients had the device removed (mean age=51 years, 58% male, mean diabetes duration=13.3 years, 55% on insulin), 20 after a full year, as planned, and 2 prematurely due to complications (1 for GI hemorrhage at 10 weeks and 1 due to liver abscess at 7 months). The complications resolved in both cases after removal. Among the 31 treated patients, mean HbA1c decreased by 2.3%, weight by 15.6 kg, systolic blood pressure by 12.4 mmHg (each $p<0.001$) (Table 7), and ALT (from 33.5 to 18.8 U/L, $p<0.001$), the latter likely reflecting reduced liver fat content. In the 17 patients on insulin, median total daily dose decreased from 100 to 30 units ($p=0.003$), with 6 (35%) discontinuing insulin entirely. Of 17 patients who had reached 6 months post Endobarrier™, 11 (65%) experienced sustained improvement in their metabolic status. Of the 6 whose weight and/or HbA1c deteriorated after removal, 5 (83.3%) had coexisting severe depression. Most (94%) patients indicted that they would be extremely likely to recommend this service to friends and family. We recall that this device, which is approved in several parts of the world, had its development program in the US delayed due to the emergence of hepatic abscesses as an adverse event during clinical trials. Other invasive and semi-invasive devices used in obesity are listed in Table 8.

Table 7. Change in Body Weight and Other Endpoints after EndoBarrier™ Treatment of Diabesity

Parameter	*Baseline*	*At Removal*	*Difference*	*p-value*
Weight, kg	120.5 ± 28.3	104.9 ± 29.4	-15.6 ± 9.2	<0.001
BMI, kg/m^2	41.5 ± 8.7	35.8 ± 8.8	-5.7 ± 3.5	<0.001
HbA1c, %	9.6 ± 2.1	7.3 ± 1.1	-2.3 ± 2.2	<0.001
Systolic blood pressure, mm Hg)	137.3 ± 13.7	124.9 ± 15.8	-12.4 ± 17.1	<0.001
Total daily insulin dose, median (IQR) units, n =17	100 (40-130)	30 (0-62)	-70	0.003

Table 8. Devices for Treatment of Obesity

Product	*Manufacturer*	*Mechanism Leading to Weight Loss*
FDA-Approved:		
vBloc (delivered via the Maestro System)	EnteroMedics Inc.	■ Electrical stimulator is placed in the abdomen to block abdominal vagal nerve activity between the brain and stomach; increases satiety
Aspire Assist	Aspire Bariatrics, Inc.	■ Tube is inserted between the stomach and outside of abdomen to drain food
EndoBarrier™ – duodeno-jejunal bypass liner	GI Dynamics	■ Reduces duodenal absorption by minimizing exposure of food to duodenal mucosa
Intragastric balloon		■ Inflatable balloons are placed in the stomach; increase satiety and reduce food intake
■ ReShape Integrated Dual Balloon System	ReShape Medical, Inc	
■ ORBERA™ Intragastric Balloon System	Apollo Endosurgery, Inc.	
■ Obalon Balloon System	Obalon Therapeutics, Inc.	
Investigational:		
Gastric pacemaker		■ Increases satiety
Duodenal mucosal resurfacing		■ Thermal ablation reduces absorptive capacity of duodenum

Given that obesity underlies many of the pathophysiological mechanisms that predispose to diabetes and several of its consequences, there is a need to continue developing safe and effective treatment approaches.

Two for the Price of One?

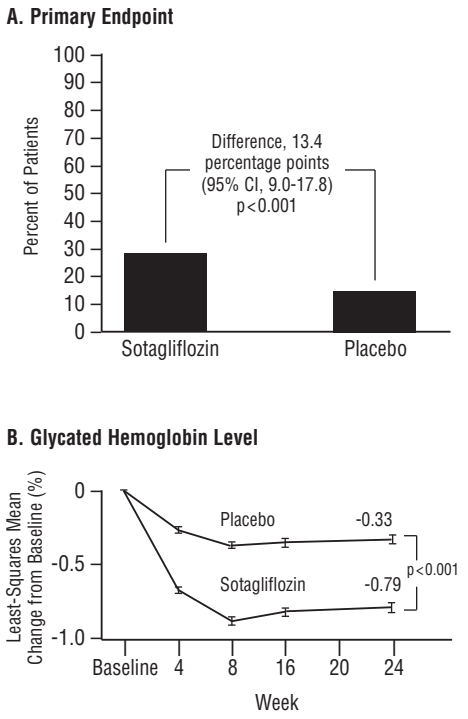
Sotagliflozin,* a dual SGLT-1 and SGLT-2 inhibitor, was the focus of discussion in a session entitled, "An Emerging and Innovative Therapeutic Approach in Type 1 Diabetes with Dual SGTL-1 and SGLT-2 inhibition: The Sotagliflozin Clinical Program." Clifford Bailey, Birmingham, UK initiated the session describing the unique mechanism of action of sotagliflozin, which blocks both SGLT-1 and SGLT-2 co-transporters. SGLT-1 is found mostly in the intestines, some muscle tissues, and a small amount in the kidneys; it has a high affinity but low capacity for

glucose transport. SGLT-1 enables glucose absorption in the small intestine and contributes (~10%) to the reabsorption of glucose filtered by the kidney. Inhibition of SGLT-1 delays and decreases glucose absorption in the proximal intestine, improving postprandial glycemic control. SGLT-2 resides almost entirely in the kidney and has a low affinity but high capacity for glucose transport. SGLT-2 is responsible for the majority (~90%) of glucose reabsorption from the glomerular filtrate in the proximal nephron. Bailey then described the history of the development of SGLT inhibitors, beginning with the discovery of phlorizin in 1835 to present day availability of three commercially available SGLT-2 inhibitors in the US and EU. He identified their known attributes in Type 2 diabetes: insulin-independent action, persistent glucosuria, sustained decrease in HbA1c and body weight, mild osmotic diuresis, and blood pressure reduction. Bailey then suggested these outcomes are also of value in Type 1 diabetes, and dual inhibition may potentially enhance these benefits further.

Julio Rosenstock, MD, University of Texas Southwestern Medical Center, US described in detail the unmet needs for patients with Type 1 diabetes and what he believes to be the absolute necessity of adjunctive therapy to insulin. Despite the great advances in insulin therapy with respect to insulin analogs, pumps, and closed-loop systems, these require intensive monitoring and a significant amount of work for the patient and the specialist provider. This is evident in that only approximately a third of patients with Type 1 diabetes attain target HbA1c levels. Additionally, glucose variability is high, severe hypoglycemia remains a concern, and cardiovascular risk is approximately 5-6 times higher than in the normal population. The frequency of DKA events is estimated at ~5% annually. Dr. Rosenstock then identified the limited value of unlabeled adjunctive therapy, specifically identifying the disappointing results of adjunctive metformin in the REMOVAL trial (Petrie, *et al. Lancet Diabetes Endocrinology*, 2017). Phase 2 results of the inTandem clinical program provide proof-of-concept data that sotagliflozin is of value in patients with Type 1 diabetes, demonstrating decreases in HbA1c by ~0.5%, weight loss, decreases in bolus insulin dosing, and low rates of hypoglycemia.

In a related poster presentation, Buse and US co-investigators presented data from a 24-week efficacy and safety trial evaluating sotagliflozin in Type 1 patients (abstract 885). The study, inTandem1, was a double-blind, phase 3 trial in adult patients with Type 1 diabetes (n=793) currently receiving insulin (pump or daily injections) and with an HbA1c of 7.0 -11%. Patients were randomized 1:1:1 to sotagliflozin 200 mg, 400 mg, or placebo after a 6-week optimization period. After 24 weeks, both sotagliflozin groups demonstrated significant ($p<0.001$) decreases in HbA1c compared with placebo. Additionally, the composite outcome of net benefit (defined as proportion of patients with HbA1c <7.0%, no severe hypoglycemia, and no DKA) favored the sotagliflozin groups (difference versus placebo 12% [p=0.002] for 200 mg and 22% [p<0.001] for 400 mg). These results along with a similar trial (and outcomes) conducted in the EU and Israel (inTandem2) led to the inTandem3 study.

Figure 10. Primary Endpoint and HbA1c Over Time: Tandem3 Trial of Sotagliflozin



Dr. Melanie Davies presented the results of this trial, which were simultaneously published in the *New England Journal of Medicine* (Garg *et al*, 9/13/2017). The phase 3 trial was a double-blind, placebo-controlled, multicenter, international trial evaluating sotagliflozin 400 mg daily in patients with Type 1 diabetes (n=1402) also receiving treatment with insulin (either via pump or injection). Additional inclusion criteria were age ≥18 years, Type 1 diabetes duration of at least one year, stable basal insulin dose for at least 2 weeks prior to screening, HbA1c 7-11%, and BMI ≥18.5 kg/m^2. The primary endpoint was HbA1c <7.0% at week 24 AND no episodes of severe hypoglycemia or DKA after randomization. The primary endpoint was achieved in 28.6% of patients receiving sotagliflozin and 15.2% of those on placebo (treatment difference 13.4% [95% CI: 9.0-17.8], p<0.001; Figure 10).

Secondary endpoints significantly (all $p \leq 0.002$) favored the sotagliflozin treatment arm. These included least-squares mean change from baseline treatment difference from placebo for HbA1c (-0.46%), body weight (-2.98 kg), systolic blood pressure (-3.5 mmHg), and mean daily insulin bolus dose (-2.8 units). Severe hypoglycemia rates were similar in both groups (3.0% [n=21] sotagliflozin; 2.4% [n=17] placebo). Documented blood glucose values of ≤55 mg/dl were significantly lower in those treated with sotagliflozin, however, rates of DKA were significantly higher in the treatment arm (3.0% [n=21]) versus placebo (0.6% [n=4]). Interestingly, rates of DKA and severe hypoglycemia occurred at higher rates in patients on insulin pumps (versus multiple daily injections) within the sotagliflozin arm compared with their placebo counterparts. Dr. Davies concluded by stating that sotagliflozin as an adjunct to insulin in Type 1 diabetes provides a net clinical benefit and addresses an important unmet clinical need. However, the higher rate of DKA with sotagliflozin, particularly in those receiving concomitant insulin via pump therapy, is of obvious concern.

Dr. John Buse, University of North Carolina, US, closed the session with a brief commentary. He first addressed whether there truly is an unmet need in Type 1 diabetes. Based on a recent survey from the Type 1 Diabetes Exchange Registry of ~16,000 patients (Miller *et al. Diabetes Care*, 2015), the average Hb1c is 8.4%; 28% of patients are overweight and 18% are obese; and 60% utilize insulin pumps. In the three months prior to the survey, 6% of patients experienced seizures or loss of consciousness due to seizures and 3% had at least one DKA event. Buse further emphasized the unmet clinical need by also stating that CV risk is high in Type 1 patients and is totally unaddressed by clinical trials. The second issue is whether dual SGLT-1/2 inhibitors provide a meaningful difference in Type 1 patients versus SGLT-2 inhibitors. He recognized the limitations of current data in support of SGLT-2 inhibitors in

Type 1 diabetes, noting the few studies thus far available, each with relatively small numbers. Despite the lack of meaningful studies, it is likely that glycemic control and weight loss will be similar between SGLT-2 inhibitors and the dual inhibitors, although head-to-head trials are needed to definitively address that comparison. Whether there is a potential advantage of dual therapy relative to a lower risk of severe hypoglycemia and/or DKA is unclear but Buse thought possible. However, the main message is that whenever any drug with SGLT-2 inhibiting effects is used in Type 1 diabetes (of course, still off-label), routine monitoring of ketones should be considered along with careful patient selection and education. Buse closed with stating that there is a clinical path forward for these medications in the management of Type 1 diabetes given the current data, but clearly more research is needed, with DKA remaining a key safety issue.

Obesity and Cancer Risk

Since our last update on this topic, 13 cancers are now defined as obesity-related cancers (Table 9), including post-menopausal breast, endometrial, colorectal, and renal cancer. This list was determined by 21 scientists from 8 academic centers who weighed available evidence, as part of the International Agency for Research on Cancer (IARC) Working Group, the cancer arm of the WHO (Lauby-Secretan, *NEJM* 2016;375:794-798). Dr. Andrew Renehan from the UK, who was part of this group, reported on the evidence base and nuances about the contribution of obesity to cancer risk. Whether obesity is defined by BMI or waist circumference, the correlation between obesity and cancer incidence remains strong. In describing the risk in terms of global burden, obesity is the third most common risk factor for cancer, with a population attributable fraction (PAF) of 3.6%, behind only smoking 21% and viral infections 16% (Arnold *et al., Lancet Oncology* 2015;16:36-46). However, in countries like the UK, where viral infections associated with carcinogenesis are rarer, obesity is the second most common risk factor for cancer with a PAF of 5.5%, behind smoking, 19%. In other words, the epidemiological evidence of an obesity-cancer connection is a sufficiently strong public health problem that future policies to prevent and treat obesity may be taken more seriously.

Dr. Renehan spoke about the beneficial effects of weight loss on cancer risk reduction. There are many limitations to studies examining people undergoing bariatric surgery, primarily because cancer risk is being assessed as a sub-analysis and is generally not powered appropriately. However, risk reductions of 0.58, 0.73, and 0.62 were found for cancers detected after sustained weight loss due to bariatric surgery (Renehan. *Lancet Oncology* 2009;10:640-1).

Dr. Renehan emphasized that nuances to interpreting epidemiological data on obesity-cancer risk include the influence of smoking on pathogenesis, in addition to hormone replacement therapy. Many studies do not adequately address these confounders in their methodology. Also, examining whether diabetes contributes to cancer pathogenesis is difficult due to a detection time bias. In order to detect an increased risk of cancer, an assessment period of at least 10-15 years after the diagnosis of diabetes is needed, yet difficult to obtain. At this time, diabetes is not thought to carry a separate, independent cancer risk than already established for obesity.

Table 9. Risk of Obesity-related Cancers

Cancer Site	*Relative Risk**
Endometrium	7.1 (6.3-8.1)
Esophagus: adenocarcinoma	4.8 (3.0-7.7)
Liver	1.8 (1.6-2.1)
Kidney: renal-cell	1.8 (1.7-1.9)
Gastric cardia	1.8 (1.3-2.5)
Pancreas	1.5 (1.2-1.8)
Meningioma	1.5 (1.3-1.8)
Multiple myeloma	1.5 (1.2-2.0)
Colon and rectum	1.3 (1.3-1.4)
Gallbladder	1.3 (1.2-1.4)
Ovary	1.1 (1.1-1.2)
Breast, post-menopausal	1.1 (1.1-1.2)
Thyroid	1.1 (1.0-1.1)

* Relative Risk of the highest BMI category evaluated versus normal BMI (95% CI). Adapted from Lauby-Secretan, *NEJM* 2016;375:794-798.

Epidemiological evidence is indirect in showing a risk relationship, whereas more direct evidence is needed to show a causal relationship. Hypotheses for biological mechanisms to explain the relationship between obesity and cancer risk are broadly categorized into three areas: 1) altered estrogen-progesterone hormones, 2) increased insulin-IGF-1 axis, and 3) increased inflammatory mediators and adipokines. Gut microbiota is also a new emerging area for research. Dr. Michael Pollack from Canada spoke about the evidence behind the insulin-IGF-1 axis in contributing to cancer risk, as well as the latest data as to whether metformin modulates cancer risk in people with diabetes and obesity. While more studies are likely in progress, lab experiments in human cells and in rodent models indicate that high insulin levels are the concerning factor in the setting of diabetes and obesity, not the hyperglycemia (Dool, *Endocrine-Related Cancer* 2011;18:699-709). Current paradigms are that dietary excess supports the growth of some tumors by influencing the hormonal environment, rather than the amount of energy available. In general, tumors are very effective at extracting the glucose they need, regardless of circulating glucose levels, as evidenced by increased PET uptake.

Dr. Pollack emphasized that hormone-based carcinogenesis requires 5-10 years, as opposed to chemical carcinogens that show effects in a relatively short period of time. If insulin is contributing to cancer risk, both endogenous and exogenous insulins are concerning. In 2009, concern about cancer risk with the specific insulin analogue glargine was raised, but follow-up studies have not shown any relationship with cancer risk.

Initial evidence for metformin in the prevention of cancer* led to over a 100 trials investigating metformin in the treatment of many cancers. While most studies are still pending, the results have been disappointing to date. Not surprisingly, metformin treatment did not alter outcomes for people with pancreatic cancer (Kordes *et al. Lancet Oncology* 2015). Metformin is thought to act either through decreasing insulin levels by reducing hepatic gluconeogenesis, or acting directly on tumor cells through AMPK activation and a decrease in mTOR signaling. Two organs that have higher intracellular concentrations of metformin include the gut and bladder. A new study showed that low-dose metformin was successful in reducing recurrence of colorectal polyps, in a chemoprevention strategy to reduce the incidence of colorectal adenomas (Higurashi *et al. BMC Cancer* 2012; 12:118). Bladder cancer responded to metformin treatment with a reduction in size in a mouse model (Zi, *Molecular Cancer Therapeutics* 2016; 15:1-9). In summary, metformin is unlikely to be helpful in the treatment of cancer, except potentially in specific types. However, the development of newer biguanides may afford new opportunities for cancer risk reduction and treatment.

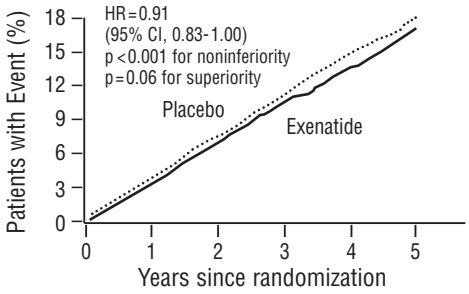
EXSCEL

On Thursday afternoon, the results of EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial were announced. This is the fourth CV outcome trial of a GLP-1 RA to report. The first three have been a mixed bag: lixisenatide in ELIXA proved neutral on MACE in an acute coronary syndrome population, and both liraglutide and the investigational semaglutide proved positive with 13% and 26% reduction in MACE, respectively.*

EXSCEL studied the weekly (ER) formulation of the original GLP-1 RA, exenatide. The study design was typical for these trials—14,752 patients with Type 2 diabetes, HbA1 6.5-10% with or without CV disease were randomized to standard care plus exenatide-ER vs. placebo injections. Over the course of a mean of 3.4 years, metabolic, CV, and safety outcomes were tracked. Notably in the trial, which had a 'pragmatic' design involving 6-month visits, the use of any other glucose-lowering agent (exclusive of GLP-1 RAs but surprisingly inclusive of DPP-4 inhibitors), either at baseline or during the trial, suffered from more than 40% of participants being off of study drug by the end of the trial. So, the true on-drug follow-up amounted to only 2.4 years, which may have impacted the trial's results.

Baseline characteristics included a mean age of 62 years, with 38% being female. The mean BMI was 31.8 kg/m^2, and HbA1c 8.0%. About 45% were on insulin and 73% had established CVD at baseline.

Figure 11. Primary CV Outcome: EXSCEL



The mean on-trial difference in HbA1c and weight between the groups was 0.53% and 1.3 kg, respectively, in favor of the GLP-1 RA. There were few other differences between the groups, both of which were to be treated to the standard-of-care for all CV risk factors. .

The primary outcome (3-point MACE) results were disappointing, with a HR for the exenatide arm vs. placebo of 0.91 (0.83-1.00; p<0.001 for non-inferiority but only 0.061 for superiority) (Figure 11). In subgroup analysis, those with age ≥65 appeared to garner more benefit with a HR of 0.80 (0.71-0.91; p=0.005 for interaction). Interestingly, the all-cause mortality HR was 0.86 (0.77-0.91; p=0.016), but given the hierarchy of statistical testing, since the primary outcome proved negative, this could only be considered nominally significant. All other secondary outcomes, including components of the primary, as well as hospitalization for heart failure were neutral.

In his summary comments, Professor Rury Holman of Oxford put the study's results in the context of the other recent GLP-1 RA trials. Using a meta-analytical approach, he found that the drugs as a group have a beneficial effect on MACE (HR 0.88 [0.81-0.95]), CV mortality (HR 0.87 [0.79-0.96]), and all-cause mortality (HR 0.88 [0.77-0.91]), but not for heart failure hospitalization. He seemed to conclude that modest differences in HRs and CIs between the trials are more likely the play of chance.

In independent commentary, Professor Francesco Giorgino from the University of Bari, Italy mostly agreed with Dr. Holman and pointed to differences in the designs of the trials, the patient populations, and the rigor with which study participants were able to maintain adherence as the likely drivers of their variable results. He left open the possibility that some molecular differences between the compounds (duration of action, homology with native human GLP-1) could be playing a role.

These are reasonable interpretations of the data, but we would add that clinical trials are conducted for reasons and need to be interpreted strictly. Accordingly, of the currently available GLP-1 RAs, only liraglutide has had a clear benefit on MACE and mortality. The all-cause mortality benefit of exenatide-ER* in EXSCEL is interesting but hard to interpret given the statistical limitations described above.

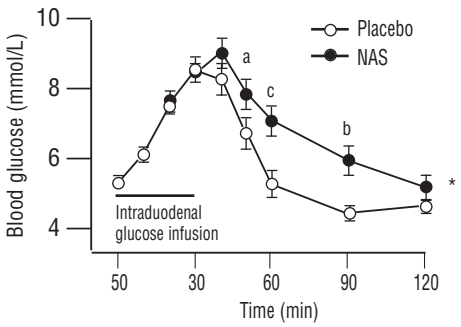
So Many Posters, So Little Time....

Perils of Artificial Sweeteners

The typical response when our diabetic patients ask us if non-sugar sweeteners are acceptable, is 'Of course!' However, prospective epidemiological studies indicate that high habitual intake of beverages containing non-caloric artificial sweeteners (NAS) may increase the risk of developing diabetes by yet-to-be determined mechanism(s).

Young *et al.* from Australia set out to assess the acute impact of artificial sweeteners on glycemia in 27 healthy subjects (mean age 27 years, BMI 24 kg/m^2). They were randomized, in a double-blind manner to dietary supplementation with a NAS combination (92 mg sucralose plus 52 mg acesulfame-K, equivalent to ~1.5 L of diet beverage/day) or placebo capsules 3 times daily before meals over 2 weeks (abstract 193). Then, after an overnight fast, the subjects underwent non-sedated endoscopy incorporating a 30-minute intraduodenal glucose infusion (30 g/150 mL, 3 kcal/minute, including 3 g of the glucose analogue 3-O-methyl glucose [3-OMG]) and biopsy collection, before and immediately after the intervention.

Figure 12. Blood Glucose Following Intraduodenal Glucose Infusion



Blood glucose responses to enteral glucose in placebo (n=13) or NAS-supplemented humans (n=14).

Non-caloric artificial sweetener (NAS) vs. placebo:
a,b,c p≤0.05, 0.01, 0.001
* p≤0.05 IAUC

NAS supplementation augmented incremental area under the curve (iAUC) for glucose absorption (serum 3-OMG) (+23%, p≤0.05) and blood glucose (Figure 12; +27%, p≤0.05), and, interestingly, attenuated the iAUC for GLP-1 (-35%, p≤0.05) compared to baseline. In contrast, none of these measures were altered with placebo. These study findings suggest that non-sugar sweeteners may in fact have a deleterious impact on acute glycemic response to carbohydrate ingestion and suggest an exaggerated postprandial glycemic excursions in high habitual NAS consumers—which could predispose to Type 2 diabetes.

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

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Robert S. Sherwin, MD
Editors, Yale School of Medicine
New Haven, Connecticut

Diabetes 2017 Test

***V**olume 36*

The post-test and evaluation must be completed on-line (not by US mail or fax) at www.goo.gl/6s934t.

1. Which of the following statements about SGLT-2 inhibitors is *false*?
   a. They lower blood glucose and HbA1c by decreasing glucose reabsorption in the proximal nephron, inducing glycosuria.
   b. They result in modest reductions in body weight and blood pressure.
   c. Neutral effects on progression of chronic kidney disease were observed in the EMPA-REG OUTCOME cardiovascular (CV) outcomes study.
   d. Their experimental use in patients with Type 1 diabetes has resulted in diabetic ketoacidosis in some individuals.

2. Early reports of diabetic ketoacidosis (DKA) from clinical trials of SGLT-2 inhibitors and during off-label use involving patients with Type 1 diabetes, have not been seen in patients with Type 2 diabetes.
   a. true
   b. false

3. All of the following, *except* _____, have been shown to reduce CV events in Type 2 diabetes patients.
   a. extended-release exenatide
   b. empagliflozin
   c. liraglutide
   d. canagliflozin

Questions 4-8:
Match the effect of the following glucose-lowering drugs on heart failure complications (e.g., hospitalizations) during treatment of diabetes patients.
   a. beneficial effect
   b. neutral effect
   c. adverse effect

4. some DPP-4 inhibitors
5. insulin
6. sulfonylurea
7. SGLT-2 inhibitor
8. thiazolidinedione (TZD)

9. In a study of diabetic retinopathy during pregnancy of Type 1 patients, all of the following, *except* _____, were determined to be risk factors for retinopathy progression.
   a. duration of diabetes >10 years
   b. nulliparity
   c. absence of retinopathy before pregnancy
   d. HbA1c increase between preconception and first trimester

10. According to study results reported at the *2017 EASD* meeting, screening for gestational diabetes should be implemented for high-risk women during the first trimester, especially in those who are obese and have a fasting plasma glucose between 100-125 mg/dL at the first prenatal visit.
   a. true
   b. false

11. Impaired awareness of hypoglycemia among patients with diabetes is associated with autonomic dysfunction.
   a. true
   b. false

12. Which of the following statements about hypoglycemia is *false*?
   a. The incidence of severe hypoglycemia increases with longer duration of disease.
   b. Data presented at the *2017 EASD* meeting showed poor results with intranasal glucagon for treating severe hypoglycemia.
   c. In a sub-group analysis of the LEADER trial (CV outcomes trial of liraglutide vs. placebo), patients with severe hypoglycemia were twice as likely than those without events to experience major CV events, CV death, and all-cause death.
   d. Hypoglycemia events are associated with long-term cognitive dysfunction.

13. In a study of 28 obese patients, (non-interventional) transcranial magnetic stimulation to the prefrontal cortex and insula resulted in significant weight loss following 15 daily sessions.
   a. true
   b. false

14. According to results of a study by Nielsen *et al.*, modification in gut microbiota composition may account for not only metformin's glucose-lowering properties, but also its adverse gastrointestinal effects.
   a. true
   b. false

15. Diabetes is thought to carry a separate, independent cancer risk than already established for obesity.
   a. true
   b. false

Questions 16-20:
Identify the most common adverse effect(s) with each of the following glucose-lowering drug/drug classes (each answer may be used more than once):

16. sulfonylurea
17. thiazolidinedione (TZD)
18. metformin
19. SGLT-2 inhibitor
20. GLP-1 receptor agonist

   a. genital infections, polyuria, dehydration
   b. gastrointestinal symptoms
   c. edema/weight gain
   d. hypoglycemia
   e. hyperkalemia

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