Diabetes 2018

Volume 38

Highlights from the
54th Annual Meeting of the European Association for the Study of Diabetes

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Diabetes 2018

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Diabetes**2018**

From the 54th Annual Meeting of the European Association for the Study of Diabetes

***O**ctober 2018*

Dear Colleague:

Time restraints prevented many of you from attending the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD) which was held a few weeks ago in Berlin, Germany. Therefore, we developed ***Diabetes 2018*** so that important information presented at the Conference could be shared with you on a timely basis.

Diabetes 2018, a newsletter CME program, is being offered to you by Yale School of Medicine with the support of an educational grant from *Medtronic.* This booklet contains three ***Diabetes 2018*** 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 2018 to July 31, 2019.

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

Sincerely,

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Educational Needs

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

Learning Objectives

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

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

Target Audience

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

Educational Methods

The online ***Diabetes 2018*** Monograph (containing all of the newsletters, a program highlights summary from the program co-editors and a sample post-test), evaluation and post-test will be available online at https://yale.cloud-cme.com/aph.aspx?EID=8735&P=3000&CaseID=393, within the Content and Test folder. The post-test must be completed on-line (not by US mail or fax).

Evaluation

An online 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 5 *AMA PRA Category 1 Credit(s)*™ 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*™.

Table of Contents

Diabetes**2018**

Editors' Summary

In this issue of the ***Diabetes 2018*** monograph, we summarize important new diabetes information that was presented at the *54th Annual Meeting of the European Diabetes Association for the Study of Diabetes (EASD)* in Berlin, Germany.

We want to highlight two symposia that book-end the progress made over the last two decades in our understanding of Type 2 diabetes and its treatment—one, a reprise of learnings from the United Kingdom Prospective Diabetes Study (UKPDS) program, and the other, a summary of updated 2018 ADA/EASD joint guidelines for glycemic management in Type 2 diabetes (http://care.diabetesjournals.org/content/early/2018/09/27/dci18-0033).

UKPDS, a landmark 20-year, multicenter, randomized, controlled outcome trial of different blood glucose and blood pressure therapies in >5,000 patients with newly diagnosed Type 2 diabetes, was launched in 1977 and completed in 1997 (UKPDS 8, Diabetologia 1991;34:877-89). Patients were randomized to conventional glucose control, with the aim of lowest fasting glucose attainable with diet alone, or to intensive glucose control, aiming for fasting glucose <108 mg/dL with monotherapy (i.e., sulfonylurea, basal insulin, or metformin.

The key findings of UKPDS were:

- At diagnosis, half of Type 2 diabetes patients had complications, identifying the need to find them earlier.
- Hyperglycemia is an independent risk factor for coronary heart disease.
- Hyperglycemia is progressive, due to declining beta-cell function.
- Improved glucose control can substantially reduce the risk of microvascular disease (~25%) and perhaps macrovascular disease (~15%).
- The glycemic "legacy effect" means that glucose-lowering therapies need to be introduced as early as possible to maximize their benefit.
- Metformin can substantially reduce cardiovascular (CV) and all-cause mortality,* supporting it as foundation therapy in treatment guidelines.
- Hyperglycemia and hypertension are "bad companions" in diabetes.
- While improved blood pressure control by itself reduces the risk of microvascular disease and stroke, combined with improved glucose control it leads to additive benefits.
- More effective glucose control can be achieved with earlier introduction of combination therapy.
- Nephropathy is a major risk factor for cardiovascular disease (CVD) and premature death.

Fast-forward 21 years, and many of the concepts first identified by UKPDS and elaborated upon by countless randomized, controlled trials conducted since then are reflected in the "hot-off-the presses" 2018 ADA/EASD joint guidelines for glycemic management in Type 2 diabetes.

Major consensus opinions reflected in these guidelines include:

- Care of diabetes must be patient-centered.
- Lifestyle change, weight loss, and physical activity are key. Metformin is the preferred initial anti-hyperglycemic medication.
- Stepwise addition of glucose-lowering drugs is preferred to initial combination therapy (but consider the latter when HbA1c is >1.5% above target).
- Choice of medication after metformin is based on patient preferences and clinical characteristics, especially CVD, other co-morbidities, and risk for specific adverse effects, particularly weight gain, hypoglycemia, safety, tolerability, and cost.
- Substantial new data have been published in the last 3 years (since the last iteration of these guidelines) show clear advantages of specific drugs in the SGLT2 inhibitor (i) and GLP-1 receptor agonist (RA) drug classes based on CV outcomes. If atherosclerotic CVD (i.e., coronary, cerebrovascular, or peripheral arterial disease) predominates, either an SGLT2-i (empagliflozin, canagliflozin) or a GLP-1 RA (liraglutide, semaglutide, exenatide extended release) is the preferred next choice. If heart failure predominates, however, then an SGLT2-i would be preferred. The same applies for the coexistence of chronic kidney disease (CKD), as long as sufficient renal function exists to allow use of SGLT2-i therapy.
- When injectable therapy is needed for glucose-lowering, GLP-1 RAs should be considered as the first choice over insulin. This recommendation is based on multiple trials showing equivalent glucose-lowering to insulin with less hypoglycemia, and weight loss instead of weight gain
- When insulin is chosen (because of patient characteristics), basal insulin is the preferred initial step.
- Patients unable to maintain glycemic targets on basal insulin in combination with oral medications should have intensification through the addition of a GLP-1 RA, SGLT2-i, or prandial insulin.
- Access, treatment cost, and insurance coverage should all be considered when selecting therapeutic strategies.

We anticipate that the new guidelines will be well-received. The writing committee did a formidable job in incorporating what has been learned over just the past three years in terms of the impact of new classes of glucose-lowering medications on CV and renal risk. They did not dismiss, however, older data regarding the foundational importance of glucose control overall—as proven by the UKPDS.

More details on these and other topics are found in this volume of ***Diabetes 2018***.

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

Diabetes**2018**

From the 54th Annual Meeting of the European Association for the Study of Diabetes ▪ Berlin, Germany

2015 2016 2017 **2018** 2019 2020 2021

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

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Harmonizing Across the Class?

The GLP-1 receptor agonists (RAs) are injectable agents that reduce blood glucose concentrations through several mechanisms: the glucose-dependent stimulation of pancreatic insulin secretion, suppression of glucagon, slowing of gastric emptying, and reduction in appetite. They are associated not only with sizable decreases in HbA1c but also modest weight loss and some improvement in other cardiovascular (CV) risk factors. To date, two members, the daily liraglutide and the weekly semaglutide, have been associated with reductions in CV events in high-risk patients with Type 2 diabetes (T2DM). With liraglutide in LEADER, the CV benefit included a 22% relative reduction in CV mortality. Two other members of the class have also been tested in large CV outcome trials: lixisenatide in ELIXA and exenatide ER in EXSCEL. Both of these proved neutral overall for CV complications, although the exenatide formulation resulted in a small reduction in all-cause mortality and 'just missed' the primary endpoint of major adverse CV events (MACE) ($p=0.06$).

So, while the GLP-1 RAs are increasingly popular diabetes drugs, there has been significant heterogeneity within the class as regards to their CV benefits. Into this controversy, enters HARMONY Outcomes, the CV outcome trial of weekly albiglutide.* Albiglutide is a long-acting drug (half-life of 5 days) with 97% homology to human GLP-1. It is fused to human albumin, which extends the duration of action. In phase 3 studies, the mean reduction in HbA1c with this compound was 0.6% and weight loss about 1.5-2 kg vs. placebo – less than with other members of this class. On the other hand, the drug appears to have less gastrointestinal (GI) side effects and may be among the best tolerated of currently available GLP-1 RAs.

The HARMONY Outcomes data were presented in Berlin on Tuesday morning to a capacity crowd at the EASD meeting with a simultaneous publication in the *Lancet*. Drs. Adrian Hernandez and Jennifer Green from Duke presented the background and design of the trial, while Professors Stefano Del Prato of University of Pisa, Italy and John McMurray of the University of Glasgow, Scotland revealed the glycemic and CV results, respectively.

The trial involved 9463 patients with T2DM (age ≥40 years, HbA1c >7%) with established CV disease, who were randomized to albiglutide (30 mg SQ weekly initially, increasing to 50 mg if needed for additional glucose control) vs. placebo, both on top of standard of care. The median follow-up was only 1.6 years. As is typical for these trials in diabetes, and as mandated by the FDA, the first hypothesis was that the drug was 'non-inferior' to placebo—i.e., did not increase the risk of CV events. If that hurdle was surpassed statistically, testing for actual superiority to placebo was then performed.

The mean age was 64.1 years with an average duration of diabetes of 14.1 years. 69% were male. The mean HbA1c at baseline was 8.7% and mean eGFR was 79 ml/min/1.73 m^2. 71% had coronary artery disease (CAD), 25% peripheral arterial disease (PAD), 25% cerebrovascular disease, and 20% heart failure. Patients were taking, individually, a statin (84%), aspirin (77%), ACE inhibitor (49%), and RAS blocker (33%) at baseline —so, good control of other CV risk factors (which is, of course, important in a CV outcome trial).

Metabolic Outcomes

The mean HbA1c was reduced to a greater extent with albiglutide (difference between groups at 8 months, -0.63 (95% CI -0.69 to -0.58); at 16 months the difference was -0.52, (95% CI -0.58 to -0.45). By end of study, 27.8% of albiglutide patients had a HbA1c <7% whereas this figure was 16.6% in the placebo group. Body weight was minimally decreased with albiglutide at less than 1 kg at both time points. Premature discontinuation of therapy occurred in 24.1% with albiglutide and 27.4% with placebo. Being

randomized to albiglutide decreased the likelihood of insulin being initiated, with a hazard ratio (HR) of 0.42 (95% CI, 0.33-0.53, p<0.0001). Severe hypoglycemia was rare but still occurred less often in the albiglutide group (HR 0.56 [95% CI, 0.36, 0.87).

CV Outcomes

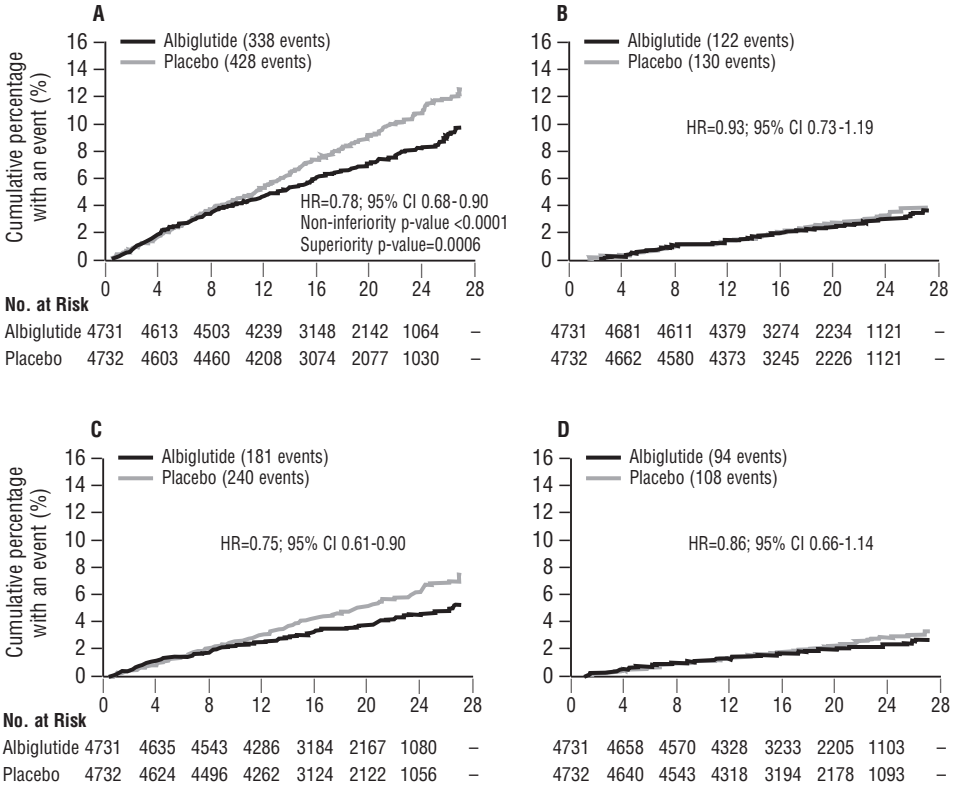
The primary outcome was time-to-first occurrence of classical 3-point MACE (CV death, myocardial infarction [MI], or stroke). The primary outcome occurred in 338 of 4731 patients assigned to albiglutide (7.1%, 4.57/100 patient-years) and 428 of 4732 patients assigned to placebo (9.0%, 5.87/100 patient-years), for a HR of 0.78 (95% CI, 0.68 to 0.90) in favor of albiglutide. These differences achieved both non-inferiority (p<0.0001) and superiority (0.0006) (Figure 1).

As for the components of MACE, the difference was mainly driven by MI (2.43 vs. 3.26/100 patient-years; HR 0.75 [95% CI, 0.61 to 0.90]; p=0.003]) and to lesser degree by stroke (1.25 vs. 1.45/100 patient-years; HR 0.86 [0.66 to 1.14]; p=0.30), with an essentially neutral effect on CV death (HR, 0.93 [95% CI, 0.73 to 1.19]; p=0.58). The latter may simply be due to the short duration of the trial, since in LEADER, the separation of the event curves for CV death did not occur until about 18 months. A pre-defined secondary outcome, the composite of CV death and heart failure hospitalization, was less common in the active therapy group but did not achieve statistical significance (HR 0.85 [0.70, 1.04]; p=0.113).

Safety

Adverse events tended to be more frequent in the placebo group. The only one that was more common with albiglutide was injection site reactions. There was a slight increase in the number of hepatobiliary events with albiglutide, as seen with other members of this class. Other GI side effects were not reported; nausea is usually more common with any GLP-1 RA, although, as mentioned, this side effect tends to occur less often with this specific compound. No differences were detected in pancreatitis events and there were no cases of medullary thyroid cancer, although admittedly the duration of exposure was brief. Microvascular complications were tracked as well, and, if anything, there was less retinopathy in the active therapy group. (Prior GLP-1 RAs, especially semaglutide, have been linked to more retinopathy, but this is likely related to strong and rapid lowering of HbA1c in predisposed individuals).

Figure 1. Time to First Occurrence of MACE



Data are (A) the primary outcome, which was a composite of death from CV causes, MI, or stroke; and each of these components individually; (B) CV death, (C) MI, and (D) stroke. Analysis are of all participants who were randomly assigned to groups. The graphs are truncated at the point at which less than 10% of patients remain at risk. HR=hazard ratio.

Clinical Implications

HARMONY Outcomes adds to a growing body of evidence indicating that the GLP-1 RAs have clear CV benefits. They are now favored by professional organizations, including the ADA, for use in those individuals with established CV disease after metformin (as are the SGLT2 inhibitors). The aforementioned differences within the class may reflect actual differences in the drugs or perhaps methodological issues between the trials. For example, ELIXA was conducted in a post-acute coronary syndrome (ACS) population. While lixisenatide was deemed to be safe (i.e., non-inferior to placebo) it could not show superiority. This may have been due to the fact that early post-ACS events are likely driven by a pathophysiological process not ameliorated by a GLP-1 RA (e.g., thrombosis). In EXSCEL, a larger that usual percentage of patients were non-adherent to therapy, possibly driven by the study's pragmatic design or by an administration device that was not user-friendly. In a recent (pre- Harmony Outcomes) meta-analysis of GLP-1 RA CV outcome trials, Bethel *et al.* found an overall 10% relative risk reduction (RRR) for MACE across the class (HR 0.90 [95% CI 0.82–0.99]; p=0.033), a 13% RRR in CV mortality (0.87 [0.79–0.96]; p=0.007), and a 12% RRR in all-cause mortality (0.88 [0.81–0.95]; p=0.002) (Bethel *et al. Lancet Diabetes Endocrinol* 2017;6:105-113).

One interesting aspect to albiglutide is that the drug, as of July 2018, is no longer being marketed by its manufacturer, a decision based on its lack of commercial success. So, while practitioners and patients will not be able to capitalize on HARMONY Outcomes' results in the near term, the trial is an important one as we develop a fuller appreciation of the CV effects of GLP-1 based therapy.

Insulin Update

The clinician caring for patients with diabetes must be well versed in currently available insulin formulations, from long-acting basal insulins to rapid-acting mealtime products, both of which try to mimic the normal insulin secretory dynamics of the endocrine pancreas. Results of numerous studies presented this week at the 2018 EASD congress further our understanding of the role of newer insulins, particularly in Type 2 diabetes.

Glargine vs. Degludec

In the open-label, treat-to-target BRIGHT trial, Cheng and multinational coworkers studied 929 insulin-naive adults with Type 2 diabetes (mean HbA1c of 8.6%, diabetes duration of 10.6 years, BMI of 31.5 kg/m^2) inadequately controlled with oral antihyperglycemic agents (OHA) ± GLP-1 RAs. They were randomized (1:1) to once-daily insulin glargine 300 U/mL (Gla-300), a concentrated from of traditional glargine, versus the newer basal insulin analogue, degludec 100 U/mL (IDeg-100) (abstract 80). Non-inferiority of Gla-300 vs. IDeg-100 was demonstrated for the primary endpoint of HbA1c change from baseline to week 24 (LS mean change from baseline: -1.64 vs. -1.59, respectively; $p<0.0001$ for noninferiority [non-inferiority margin 0.3%]).

Both insulins similarly decreased fasting plasma glucose at week 24 (-57.6 and -59.4 mg/dL, respectively), with final daily insulin doses of 0.54 and 0.43 U/kg from starting evening doses of 0.2 and 0.12 U/kg, respectively. Over the 24-week period, incidence of confirmed (≤70 mg/dL) or severe hypoglycemia was comparable, but event rates were lower with Gla-300 vs. IDeg-100, by 14% at any time of day (24 hours) and by 19% at nighttime (midnight until 6AM). Taken together, results of the BRIGHT trial show that Gla-300 provides similar glycemic control to IDeg-100, but with less hypoglycemia, in previously inadequately controlled, insulin-naive adults with Type 2 diabetes.

Self-titration of Glargine

Davies and coworkers from Europe and Japan examined patient self-titration versus physician-led titration of Gla-300 (TAKE CONTROL study) and traditional glargine (Gla-100) (AT.LANTUS and ATLAS studies) in three 24-week, multicenter, randomized studies of patients with Type 2 diabetes (abstract 825). Fasting blood glucose targets were 80-130 mg/dL in TAKE CONTROL, ≤100 mg/dL in AT.LANTUS, and ≤110 mg/dL in ATLAS. Mean baseline HbA1c ranged between 8.4% and 8.9%. Self-titration resulted in significantly improved glycemic control versus physician-led titration ($p<0.05$ for all 3 studies), without increased incidence of hypoglycemia (Table 1).

IDegAsp for Patients with Type 2 Diabetes

Gupta and multinational investigators conducted a 38-week treat-to-target trial comparing two insulin strategies involving both basal and

Table 1. Comparison of Self-Titration and Physician-Led Titration with Glargine in Type 2 Diabetes

	TAKE CONTROL 24 weeks		*AT.LANTUS 24 weeks*		*ATLAS 24 weeks*	
	Self-Titration Gla-300 n = 314	*Physician-Led Titration Gla-300 n = 317*	*Self-Titration Gla-100 n = 2,273*	*Physician-Led Titration Gla-100 n = 2,315*	*Self-Titration Gla-100 n = 275*	*Physician-Led Titration Gla-100 n = 277*
Type of population	Insulin-naïve and previously treated, Europe		Insulin-naïve and previously treated, Europe, South America, Asia, Africa, Middle East		Insulin-naïve, Asia	
Mean diabetes duration, years	12.9 (7.2)	12.8 (6.9)	12.3 (7.0)	12.3 (7.3)	10.3 (6.9)	9.1 (5.3)
Baseline HbA1c, %	8.4 (0.9)	8.4 (0.9)	8.9 (1.3)	8.9 (1.3)	8.7 (1.0)	8.8 (1.1)
Final HbA1c [change from baseline], %	7.4 (1.0) [-0.97*]	7.6 (0.9) [-0.84]	7.7 (1.2) [-1.22*]	7.9 (1.2) [-1.08]	7.3 (0.9) [-1.40*]	7.5 (1.0) [-1.25]
HbA1c, LS mean difference self vs. physician-led titration	-0.13 (-0.26 to -0.00)		—		-0.15 (-0.29 to -0.00)	
Total basal insulin dose/day, U Baseline/end of treatment/ mean change from baseline	24.1/39.7/15.6	25.7/36.9/11.2	23.5/45.0/21.6	22.3/41.0/18.7	8.2†/28.9/–	8.1†/22.2/–
Incidence of severe/symptomatic/ nocturnal hypoglycemia, %	0.6/26.3/8.0	0.3/25.6/11.4	1.1/29.7/4.1	0.9/26.3/3.2	0.7/36.0/16.4	0.7/25.6/6.5
Any treatment-emergent AE/serious AE	33.7/3.2	34.5/3.8	48.0/5.1	49.4/5.1	35.0/3.3	32.1/1.8

Data are mean (SD) unless otherwise noted.

* Statistically significantly different vs. physician-led titration.

† Starting dose.

rapid-acting insulins. In the first approach, once daily glargine (Gla-100) was used along with aspart (iAsp) given before meals. (This is often referred to as 'basal-plus' if only 1 meal is covered with aspart or 'basal-bolus' if 2 or more meals are covered). The second approach was that using an investigational premixed insulin, the combination of degludec and aspart (IDegAsp), in a 70%/30% formulation. They randomized 532 adults with Type 2 diabetes on basal insulin ± oral agents and in need of treatment intensification (HbA1c 7-10%) to IDegAsp (week 0-26; QD with largest meal; week 27-38: QD/BID with largest meals) or QD Gla-100 + iAsp (week 0-26: QD with largest meal; week 27-38: QD/BID/TID at main meals) (abstract 836). Dosing could be intensified at weeks 26 and 32 if HbA1c was above target (≥7%) during the previous week.

Both treatment groups achieved similar glycemic control at weeks 26 and 38 (-1.1 to -1.3% decrease in HbA1c). IDegAsp resulted in significantly fewer nocturnal hypoglycemia episodes (severe [ADA defined] or blood glucose-confirmed [<56 mg/dL] symptomatic episodes), lower insulin dose, and fewer injections. The investigators concluded that IDegAsp QD and BID are simple, effective treatment intensification options in Type 2 diabetes, as compared with 'basal-plus' or full 'basal-bolus' therapy. Such a strategy may be ideal in those patients who require both basal and meal-time insulins but are not capable of the more complex methods involving two different and separately administered insulins.

Simplification of Treatment with IDegLira in Type 2 Diabetes

After euglycemia is achieved with multiple daily insulin injections (MDI), there may be an opportunity to simplify insulin dosing. Taybani *et al.* from Hungary tested this approach with a fixed-ratio combination of a basal insulin (degludec) plus a GLP-1 receptor agonist (liraglutide) (IDegLira) (abstract 842). 48 adults with Type 2 diabetes were studied (mean±SD: age 65±8.6 years, BMI 32.28±6.77 kg/m^2, duration of diabetes 12.3±8.1 years). They were relatively well-controlled (HbA1c 6.48±0.65%) using MDI, with a relatively low total daily insulin dose of 40.9±11.1 units ± metformin. The patients were then switched to IDegLira and self-titrated every 3 days in 2 dose steps (each dose step contained 1 unit of insulin degludec and 0.036 mg of liraglutide), as needed, to achieve a self-measured pre-breakfast plasma glucose concentration of <108 mg/dL.

At the study's conclusion (mean, 96 days), significant reductions were noted for HbA1c (mean change of -0.25% to a mean value of 6.23%; p<0.001), body weight (mean change of -2.6 kg to a mean of 87.6 kg; p<0.001), and BMI (mean change of -1.0 kg/m^2 to a mean of 31.3 kg/m^2; p<0.001). At the end of the follow-up, the mean dose of IDegLira was 20.1 units of insulin degludec (decreased from 40.9 units at baseline visit), and 0.8 mg of liraglutide, and mean dose of metformin was 1594 mg. IDegLira ± metformin combination therapy was safe and generally well tolerated. More than half of the patients (26, 54%) had at least one episode of hypoglycemia (documented glucose <70 mg/dL or symptomatic hypoglycemia) during the month before baseline, compared with 5 (10.4%) patients during the study.

These study findings suggest that switching from low-dose MDI to IDegLira in patients with well-controlled Type 2 diabetes results in similar or better glycemic control as well as weight loss. Of course, it's hard to make much of a small, uncontrolled study. Yet, we found these data interesting. Certainly, simplifying complex treatment regimens may improve adherence and quality of life in Type 2 diabetes patients. Of course, any newer product is bound to be more expensive that older formulations, given that costs must always be considered when trying emerging therapies.

Degludec and Exercise in Type 1 Diabetes

Moser *et al.* from the UK and Austria reported on the results of a randomized crossover study they conducted to compare time spent in euglycemia among a small group of 9 patients with Type 1 diabetes (4 females, age 32.1±9.0 years, BMI 25.5±3.8 kg/m^2, HbA1c 7.2±2.8%) during 5 consecutive days of continuous moderate-intensity exercise (cycle ergometer for 55 minutes). The patients took either 100% or 75% of their usual IDeg dose (abstract 81). A 25% reduction in IDeg dose around regular exercise achieved a longer time spent in euglycemia (p=0.04) with no effect on number of hypoglycemic events (75% dose—4.8 events, 100% dose—4.7 events; p=0.91) or time spent in hypoglycemia (glucose <70 mg/dL, p=0.07) or even hyperglycemia (p=0.38). The amount of carbohydrates and dose of bolus insulin injections were similar between the two dosing regimens. The results of this study suggest that people with Type 1 diabetes should be encouraged to reduce IDeg dose by 25% when performing regular exercise on consecutive days.

Rapid Lispro in Type 1 Diabetes

Plum-Morschel and multinational investigators reported results of a 2-part double-blind Phase 1b study that compared the effect of an investigational ultra-rapid lispro (URLi; LY900014)* to that of conventional rapid-acting lispro (Humalog®) on glucose excursions (abstract 60). The ultra-rapid lispro 'kicks in' somewhat quicker than lispro (about 9 minutes sooner). In Part 1 (6-period cross-over design), postprandial glucose response to solid mixed meal tolerance tests (MMTT) with the same, individualized doses of URLi or lispro at different injection-to-mealtime intervals (-15, 0, and +15 minutes) was assessed in 30 patients with Type 1 diabetes. In Part 2 (parallel design), glucose response was assessed during 2 weeks of multiple daily dosing (immediately before a meal). Patients were stabilized overnight targeting a fasting blood glucose level of 126 mg/dL before the MMTT procedure.

URLi reduced glucose excursions (assessed as change in area under the concentration curve vs. time [ΔAUC]) vs. lispro during the first 2 hours ($\Delta AUC_{0\text{-}2h}$) and over the entire 5 hours ($\Delta AUC_{0\text{-}5h}$) of the MMTT, regardless of dose timing. At -15, 0, and +15 minutes, respectively, URLi reduced $\Delta AUC_{0\text{-}2h}$ by 103% (p=0.008), 39% (p=0.031), and 16% (p=0.096) and $\Delta AUC_{0\text{-}5h}$ by 40% (p=NS), 44% (p=0.097), and 42% (p=0.026) vs. lispro. These effects of URLi and lispro were sustained after 2 weeks of outpatient dosing (Part 2). Similar numbers of hypoglycemic events occurred between treatments during MMTTs. During 2 weeks of outpatient dosing, the number of events was numerically lower for URLi vs. lispro. These results provide preliminary evidence that URLi may improve postprandial glucose control in Type 1 diabetes at multiple meal-to-dose timing intervals.

Fast-acting Aspart and Hypoglycemia

Hypoglycemia is a ubiquitous challenge with insulin treatment in Type 1 diabetes, with nocturnal episodes particularly concerning. De Block and co-workers from Europe and the United States evaluated severe hypoglycemia with meal-time fast-acting insulin aspart* ("faster aspart") versus conventional insulin aspart (IAsp) in two large double-blind, treat-to-target, randomized Type 1 diabetes trials (52-week trial in combination with insulin detemir [n=761], and a 26-week trial in combination with insulin degludec [n=684]) (abstract 59). Faster aspart was non-inferior to IAsp based on glycemic control (HbA1c reduction from baseline) in both trials (p<0.05 in insulin detemir trial). The rate of nocturnal severe (requiring assistance of another person for corrective actions) or blood glucose-confirmed (<56 mg/dL) hypoglycemia was lower with faster aspart vs. IAsp in both trials (pooled estimated treatment rate ratio [ETR] 0.84 [95% CI: 0.72; 0.98]; p=0.02), but not for overall (pooled ETR 0.94 [0.85;1.05]) or diurnal hypoglycemia rates (pooled ETR 0.96 [0.86;1.07]). This study, in our minds, shows a very modest benefit on

hypoglycemia with the more rapid-acting version of aspart.

Insulin after Discharge

Transitional care after a hospitalization may be inadequate for older patients with diabetes, particularly for those started on insulin during their hospitalizations, who may be at increased risk for post-discharge serious adverse events.

Lipscombe *et al.* from Toronto, Canada conducted a retrospective population-based cohort study to quantify the incidence of death and hospital readmissions after discharge (between April 2004 and November 2013) for older hospitalized patients (age ≥66 years) prescribed oral glucose-lowering medications, and to compare risk of these adverse events between patients prescribed new insulin therapy versus oral agents (abstract 829). Eligible participants were dispensed a prescription for one of the two strategies within 7 days of discharge.

Of 104,525 patients, 9.2% were initiated on insulin, 4.1% died, and 26.2% had a return to hospital (emergency department visit or readmission) within 30 days of discharge. Deaths occurred in 7.1% of new insulin users, 4.9% of prevalent insulin users (i.e., prescribed insulin before admission and at discharge), 3.3% of new oral agent users (i.e., no treatment before admission), and 3.5% of prevalent oral agent users. Rates of return to hospital were 28.1% among new insulin users, 29.8% among prevalent insulin users, 25.1% among new oral agent users, and 25.0% among prevalent oral agent users. After adjustment for covariates, new insulin users had a 52% higher 30-day risk of death (adjusted hazard ratio, aHR 1.52, 95% CI, 1.39 to 1.67) and a 16% higher 30-day risk of return to hospital (aHR 1.16, 95% CI 1.11 to 1.21) than prevalent oral agent-treated patients. Findings were similar for hospital visits for hypo/hyperglycemia (Table 2). The investigators concluded that better discharge planning and transitional care are needed for older hospitalized patients treated with insulin. Further study is needed to determine appropriate interventions to reduce adverse outcomes after insulin initiation in older hospitalized patients, so that the benefits of effective diabetes management attained during hospitalization can be maintained after patients are discharged.

These and other presentations this week provide new and important information about emerging insulin strategies.

Table 2. All-Cause Mortality and Return to Hospital: Comparison of Risks Among Patients Treated with New Insulin Therapy Versus Oral Agents

Outcomes	*Prevalent OHA (Referent) n = 62,018*	*New Insulin n = 9,592*	*Prevalent Insulin n = 25,203*	*New OHA n = 7,712*
All-cause mortality, 30 days				
Events, n (%)	2,137 (3.5%)	685 (7.1%)	1,224 (4.9%)	251 (3.3%)
Out-of-hospital deaths, n (%)	1,026 (48.0%)	412 (60.1%)	638 (52.1%)	100 (39.8%)
Inpatient deaths, n (%)	1,111 (52.0%)	273 (39.9%)	586 (47.9%)	151 (60.2%
Unadjusted HR (95% CI)	1.00	2.12 (1.94 – 2.31)	1.42 (1.32 – 1.52)	0.94 (0.83 – 1.08)
Adjusted HR (95% CI)	1.00	1.52 (1.39 – 1.67)	1.11 (1.03 – 1.20)	1.23 (1.08 – 1.40)
Return to hospital (any ED visit or hospital admission) 30 days				
Events, n (%)	1,5386 (25.0%)	2,644 (28.1%)	7,425 (29.8%)	1,927 (25.1%)
ED visits only, n (%)	7,828 (50.9%)	1,322 (50.0%)	3,636 (49.0%)	1,049 (54.4%)
Readmissions, n (%)	7,558 (49.1%)	1,322 (50.0%)	3,789 (51.1%)	878 (45.6%)
Unadjusted HR (95% CI)	1.00	1.14 (1.10 – 1.19)	1.22 (1.19 – 1.25)	1.00 (0.96 – 1.05)
Adjusted HR (95% CI)	1.00	1.16 (1.11 – 1.21)	1.14 (1.11 – 1.18)	1.04 (1.00 – 1.10)
Return to hospital (ED visit or hospital admission, for hypo/hyperglycemia) 30 days				
Events, n (%)	302 (0.5%)	113 (1.2%)	289 (1.2%)	63 (0.8%)
Unadjusted HR (95% CI)	1.00	2.47 (1.99 – 3.06)	2.37 (2.02 – 2.79)	1.68 (1.28 – 2.20)
Adjusted HR (95% CI)	1.00	2.40 (1.92 – 3.00)	2.31 (1.95 – 2.73)	1.68 (1.28 – 2.21)

OHA=oral hypoglycemic agent

Feeling Low...

We know that hypoglycemia is a rate-limiting step in diabetes management since it prevents many patients from achieving their glucose targets, especially those patients with more long-standing disease using insulin injections. It has also become recently recognized that hypoglycemia, particularly severe hypoglycemia, is linked to increased CV mortality, although a precise cause-and-effect relationship remains unclear. Newer glucose-lowering agents reduce the risk of hypoglycemia. Yet, all patients with Type 1 diabetes and many patients with Type 2 diabetes require insulin therapy. In these individuals and those using insulin secretagogues, hypoglycemia is essentially unavoidable—although the risk can always be mitigated. Understanding risk factors, implications, and prevention/treatment strategies is an increasingly important component of diabetes care. Several presentations this week explored these very issues.

Au *et al.* from Canada were interested in non-severe hypoglycemia as a common event in patients with Type 2 diabetes treated with insulin or insulin secretagogues, like sulfonylureas (abstract 912). Although this complication of diabetes management does not get as much attention in the literature as severe hypoglycemia, it still results in fear, reduced quality of life, and weight gain, and impedes optimal control of blood glucose. Of course, non-severe hypoglycemia also increases the risk of severe hypoglycemia. It is defined as any blood glucose <70 mg/dl associated with symptoms but not incapacitating the patient to the point where he or she requires the assistance of another individual. This condition is under-reported in clinical trials and is often 'under the radar screen' to most clinicians.

In the InHypoDM study, the investigators recruited 432 patients with Type 2 diabetes on insulin or insulin secretagogues from an on-line survey. A validated questionnaire was used to elicit self-reported frequencies of non-severe hypoglycemia and clinical and socio-demographic characteristics. Multivariable negative binomial regression identified risk markers for this condition.

The cohort was 56% male with a mean age of 53±15 years and mean diabetes duration of 11.7±7.8 years. More than half the participants (54.2%) reported having experienced at least one episode over the prior 30 days. The incidence rate was determined to be 28.7 (95% CI, 26.9 to 30.5) events per person per year. Multivariable analysis suggested that unemployed status (OR 1.46, 1.01-2.10, p=0.04) and the presence of other medical comorbidities (OR 2.08 1.52-2.84, p<0.0001) were major risk factors. Lower income (p<0.0001), higher HbA1c (p=0.0067), longer disease duration (p=0.0005), and younger age (p<0.0001) were other, though more modest risk indicators.

The investigators concluded that non-severe hypoglycemia was extremely common in patients with Type 2 diabetes treated with certain glucose-lowering agents. They identified several simple clinical and socio-demographic features that increase its frequency and felt that these may be helpful to identifying patients at risk in clinical practice. Of course, when possible, using agents with lower risk of hypoglycemia will further decrease the incidence.

The impact of hypoglycemia on the CV system has become a hot area of investigation since low blood glucose concentrations were found to be much more common in the intensive management arm of the ACCORD trial. Moreover, it was realized that randomization to this strategy increased the risk of CV mortality. A cause-and-effect relationship between these two phenomenon has been suspected, but never proven. Sianni and Greek colleagues studied 278 patients with Type 2 diabetes, a history of ischemic stroke, and paroxysmal atrial fibrillation (PAF) on anticoagulation (abstract 903). All patients underwent ECG, Holter monitoring, and brain CT in order to establish the presence of both PAF and prior stroke. They then proceeded to measure fasting and 2-hour post-prandial blood glucose with a home meter over a period of 3 years (frequency not described). Repeat ECG was performed every 3 months and additionally if the patient presented to the study sites with symptomatic palpitations or rapid pulse rate.

During the follow-up, 166 patients (60%) were found to have tachyarrhythmias in the context of PAF; the remaining 112 (40%) did not. In the first group, 133/166 patients (80%) had 10-18 episodes of hypoglycemia per patient (averaging 2-4 episodes/month). In the second group (i.e., without symptomatic tachyarrhythmias), only 14 of 112 (13%) had hypoglycemia (occurring between 8-10 episodes per patient, averaging 0-2 per month). The difference between the two groups was of borderline statistical significance (p=0.04).

The investigators concluded that hypoglycemia increases the risk of tachyarrhythmias in the setting of PAF in stroke patients with Type 2 diabetes and that avoiding hypoglycemia was important in this population. While interesting, we feel this study has a suboptimal design, identifying tachyarrhythmias only by patient report or on infrequently performed ECGs. Their mechanism to identify hypoglycemia was similarly intermittent. A better design would have included some form of 24-hour monitoring devices (Holters, continuous glucose monitors ([CGM]) after the baseline visit to better capture these respective events. Nonetheless, the investigators' findings are consistent with the known stress response (including catecholamine release) that is induced by hypoglycemia, with potential resultant predisposition to a variety of arrhythmias.

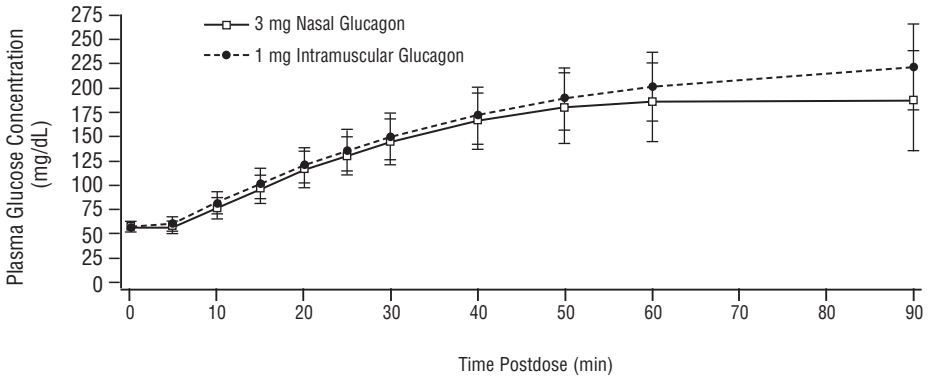
Exercise is felt to induce hypoglycemia especially in those with Type 1 diabetes. However, exercise is important to maintain fitness and improve CV health, and it is currently recommended that patients with diabetes try to maintain at least 150 minutes of moderate-to-vigorous physical activity each week. Taylor and UK collaborators sought to determine the "real-world" impact of such activity on the risk of hypoglycemia (abstract 909). They studied 47 patients with Type 1 diabetes (27 men, 20 women, mean age 40 ±11 years, diabetes duration 21±11 years, BMI 25.3±3.4 kg/m^2, HbA1c 7.4%±0.6%). In this study, the investigators did use CGM, with the devices placed for 7 days; various parameters of glycemic control, including hypoglycemic excursions and 'time in range', were tracked. Physical activity was assessed using accelerometers, which were worn by each participant. Moderate-to-vigorous activity of >10 minutes was recorded.

On average, the patients achieved 26.8±20.7 minutes of moderate-to-vigorous physical activity per day. There was wide variation, with 24 (51%) of the participants completing >150 minutes across the 7 days and 4 participants being extremely inactive, completing none. Interestingly, absolutely no correlations were found between the amount and degree of physical activity and any CGM glycemic parameter, including hypoglycemia: time spent <54 mg/dl, r=-0.038 (p=0.805); hyperglycemia: >250 mg/dl, r=-0.154 (p=0.313); time in range (54-180 mg/dl) r=0.207 (p=0.172); or outside this range, r=-0.207 (p=0.172). There also appeared to be no associations between physical activity and glycemic variability measures (standard deviation [SD] of sensor glucose, r=-0.045, p=0.771; coefficient of variation (CV) of sensor glucose, r = 0.122, p=0.426). Neither could they identify differences between individuals at the extremes of physical activity.

So, in this first observational study comparing glycemic control across a spectrum of exercise, the investigators found no increased rates of hypoglycemia in those individuals who were the most active, including those achieving the recommend 150 minutes per week of moderately vigorous physical activity.

Of course, this study may simply indicate that patients who are physically active are likely to be properly educated on avoiding hypoglycemia,

Figure 2. Mean (±SD) Plasma Glucose after Singe-Dose Nasal or IM Glucagon



since supplemental calorie intake and insulin dose adjustments were not measured. In addition, since patients knew about the study's hypothesis, it is likely that they made greater efforts to avoid low blood sugar. Nonetheless, it suggests that our more physically active patients may not be at greater risk of hypoglycemia (at least if they are wearing CGMs!).

Hypoglycemia is typically treated with oral, readily absorbed carbohydrates. In those circumstances where hypoglycemia is severe, swallowing may be impaired and, traditionally, glucagon has been used, typically administered by another individual. This involves reconstitution of a solution and then an intramuscular injection—considered cumbersome by many people. Nasal glucagon* is a new formulation of this hormone that is more easily administered. The single-use device under investigation sprays 3 mg of glucagon as a dry powder.

Suico and American/European colleagues studied 66 patients with Type 1 diabetes, randomizing them in a crossover fashion to treatment of experimental hypoglycemia with either injectable or nasal glucagon (abstract 150). Hypoglycemia (plasma glucose <60 mg/dl) was induced with IV insulin infusion. Five minutes after the insulin infusion was stopped either 3 mg of nasal or 1 mg of IM glucagon was administered. Successful treatment was defined as an increase in plasma glucose to ≥70 mg/dl or an increase of at least 20 mg/dl from the glucose nadir. This was a non-inferiority trial with the upper and lower bounds of the confidence limits set at <10% difference.

Each patient studied achieved successful treatment of hypoglycemia by 25 minutes. The mean time to resolution was 11.4 minutes with the nasal formulation and 9.8 minutes with the IM injections. Similar glucose responses to both agents are displayed in Figure 2. There were no serious adverse events, and minor adverse events were similar between the groups. The most common were nausea, vomiting, and headache (nasal group: 31%, 14%, and 16%; IM group: 42%, 17%, and 10%.) With nasal glucagon there were, however, some common, local side effects such itching of the eyes, nose or throat, tearing, nasal congestion, and sneezing.

The investigators felt that their data indicated this new formulation to be as efficacious as traditional glucagon injection, with a few additional minor side effects. Depending on cost, nasal glucagon may become an attractive future option for patients.

So Many Posters, So Little Time....

Cluster Subgroups or Simple Clinical Characteristics as Predictors of Drug Response and Diabetes Progression?

Traditionally, diabetes has been distinguished into three main types: Type 1, Type 2, and "secondary diabetes", the latter term used when hyperglycemia is the direct result of separate disease process, such as acromegaly, pancreatic disease, or that related to certain drugs, like steroids. Monogenic forms of diabetes, including maturity onset diabetes of youth (MODY), due to genetic abnormalities in beta-cell function have been classified as "secondary diabetes," but are probably misplaced here. Of course, within Type 2 diabetes, there are multiple phenotypes—the obese, the lean, the more insulin resistant, and the more insulin deficient. Recently, investigators have tried to add further clarity to this heterogeneity by proposing sub-categories of Type 2 diabetes.

For example, in a recent "cluster analysis" of clinical and biochemical data gathered close to Type 2 diabetes diagnosis in 8,980 Scandinavian patients, Ahlqvist *et al.* developed the concept of 5 novel subgroups (Table 3) that have significantly different patient characteristics as well as risk for long-term diabetic complications (*Lancet Diab Endo* 2018;6:361-9). If these subgroups have clinical utility, they might be targeted with different treatment and follow-up strategies.

This new concept was tested by Dennis and coworkers from the UK, who used data from the 4,351 participants with newly diagnosed Type 2 diabetes enrolled in the 2006 ADOPT trial. They had been randomized to either metformin, the sulfonylurea glyburide, or the thiazolidinedione (TZD) rosiglitazone for up to 5 years. The original trial was designed to compare durability of effectiveness, with those assigned to the TZD having the most sustained improvement in HbA1c. The investigators sought to determine if they could replicate the subgroups derived from the cluster analysis of Ahlqvist *et al.* Then, they tested the predictive ability of these clusters for key patient outcomes—HbA1c response over 1 year, HbA1c progression from year 1 to 5, and 5-year risk of chronic kidney disease (CKD) stage 3. They subsequently compared the results with regression models using three routine clinical measures as continuous variables (age of diagnosis, baseline HbA1c, and BMI) (abstract 46).

Table 3. Clusters of Type 2 Diabetes Patients with Different Characteristics and Risks of Diabetes Complications

Cluster	*Label*	*Characteristics*
1	severe autoimmune diabetes (SAID)	early-onset disease, relatively low BMI, poor metabolic control, insulin deficiency, and presence of GADA
2	severe insulin-deficient diabetes (SIDD)	similar to Cluster 1, but GAD-negative
3	severe insulin-resistant diabetes (SIRD)	insulin resistant (high HOMA2-IR index) and high BMI
4	mild obesity-related diabetes (MOD)	obese, modest metabolic derangements (not insulin resistant)
5	mild age-related diabetes (MARD)	older than patients in other clusters, but showed, similar to Cluster 4, only modest metabolic derangements

The 5 cluster-derived subgroups within ADOPT replicated closely, in both prevalence and clinical characteristics, those previously reported by Ahlqvist *et al.* HbA1c response up to 1 year varied by cluster subgroups for each drug, whereas the model incorporating the routine clinical measures (age, HbA1c, BMI) had far greater predictive ability (metformin: R^2 0.24 for clusters versus 0.41 for the routine clinical measures [$p<0.001$]; sulfonylureas: R^2 0.27 vs. 0.41 [$p<0.001$]; TZDs: R^2 0.17 vs. 0.35 [$p<0.001$]). The clinical measures also seemed to be as good as clusters for predicting HbA1c progression overall and better than clusters for predicting the development of CKD. The investigators concluded that, in the protocol-driven conditions of the ADOPT clinical trial, simple and easily obtained clinical measures may be the best guide to defining a patient's progression and drug response, not the more complex cluster-derived subgroups.

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

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Diabetes**2018**

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SGLT2 Inhibition: Beyond Glucose

The sodium glucose cotransporter 2 (SGLT2) inhibitor (i) class of medications was the subject of numerous symposia and abstract presentations at this year's EASD. Originally developed for glycemic control due to their glucosuric effects, subsequent investigations of this class demonstrated CV benefits and kidney protection. An afternoon symposium focused on the role of SGLT2 inhibition in the kidney.

Dr. Hiddo Heerspink, from the Netherlands, presented the history of SGLT2 inhibitor development and reviewed the growing body of evidence supporting renal protection such as decreased albuminuria and halting the progression of declining eGFR, each of which occur independent of glycemic control. In contrast, another newer class of diabetes medications, the DPP-4 inhibitors, have shown some effects on albuminuria but not much effect on the decline in renal function.

Dr. David Cherney, Toronto, Canada, followed with perspectives on potential mechanisms for renal protection along with rationale for SGLT2 and DPP-4 inhibitor combination therapy. With respect to SGLT2 inhibition, the mechanism appears to be hemodynamic and unrelated to glycemic control. While a complex mechanism, the general pathway is normalization of solute (sodium) delivery to the macula densa, increasing adenosine production. Activation of the adenosine receptor reverses afferent arteriole vasodilation commonly associated with diabetic kidney disease. Thus, 'tubuloglomerular feedback (TGF)' is restored. The role of DPP-4 inhibition is much less understood, however, the hypothesis for a complementary effect with SGLT2 inhibition may be mediation of distal natriuresis and/or suppression of markers of inflammation such as interleukin (IL)-1beta.

Given these hypotheses, the presenters anxiously await the results of the DELIGHT trial. This is an exploratory phase 2/3 study comparing the efficacy and safety of dapagliflozin with or without the DPP-4 inhibitor saxagliptin in patients with Type 2 diabetes and chronic kidney disease with albuminuria already treated with an ACEi or ARB.

Several presentations this week assessed the so-called non-glycemic benefits of the SGLT2 inhibitor class. In a *post-hoc* analysis of the EMPA-REG OUTCOME trial, Ruggenenti and international colleagues investigated the impact of empagliflozin in patients with Type 2 diabetes and established CV disease and nephrotic-range proteinuria (abstract 1036). Using the criteria for nephrotic-range proteinuria as defined by Kidney Disease: Improving Global Outcomes (KDIGO), patients with a urine albumin:creatinine ratio (UACR) ≥2200 mg/g at baseline were identified (placebo, n=42; empagliflozin 10 or 25 mg, n=70). A random coefficient model was used to assess treatment differences in the average rate of annual loss of estimated GFR (eGFR) over time. Additionally, the difference in all-cause hospitalization (ascertained by investigator serious adverse event reporting) between groups was evaluated using a Cox proportional hazards model.

Groups were well matched at baseline with respect to UACR and eGFR with each demonstrating a fall in eGFR for the first four weeks of the study. However, from week 4 to week 178, a steeper decline in eGFR was observed with placebo than with the pooled empagliflozin (10 or 25 mg) group (Figure 3). Yearly decline of eGFR was 6.1 ml/min/1.73m^2 slower with empagliflozin (p=0.0098) when compared with placebo. A significant decrease in all-cause hospitalization was also observed in the empagliflozin arm (HR 0.53 [0.30-0.93], p=0.0263). From this *post-hoc* analysis, empagliflozin may be a viable treatment option to slow renal decline and reduce all-cause hospitalizations in those with existing cardiovascular disease and nephrotic-range proteinuria.*

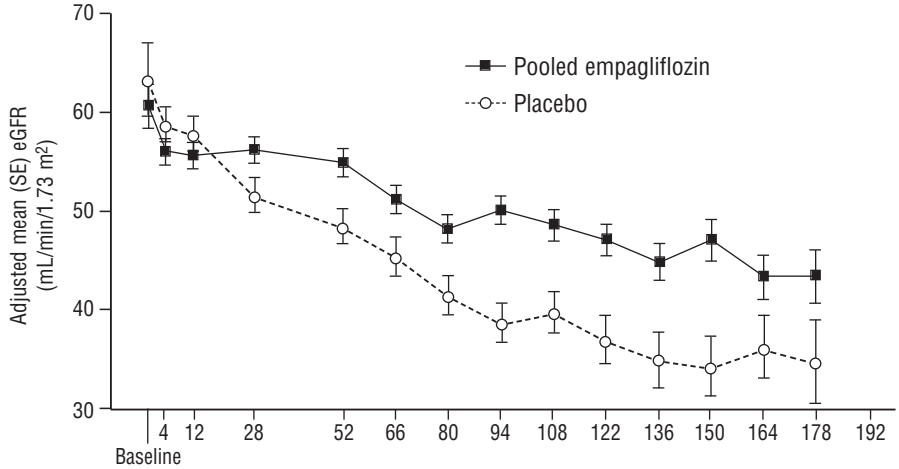
Data from the EMPA-REG OUTCOME trial was also further analyzed by residual CV risk at baseline to determine its impact on CV mortality and heart failure (HF) hospitalization rates. Fitchett and co-investigators from Canada, US, and Germany used the 10-point TIMI Risk Score for Secondary Prevention (TRS 2P) categorizing patients (n=7,020) as low (12%), intermediate (40%), high (30%),

and highest (18%) residual CV risk (abstract 110). P-values for each subgroup interaction were determined from tests of heterogeneity of treatment group differences among subgroups with no adjustment for multiple testing. In all categories of outcomes (CV death, all-cause mortality, hospitalization for heart failure, and hospitalization for heart failure or CV death), empagliflozin demonstrated a consistent benefit regardless of baseline risk.*

In another *post-hoc* analysis involving the SGLT2 inhibitor, canagliflozin, researchers from the CANVAS program, Perkovic et al., evaluated CV outcomes with respect to baseline kidney function (abstract 75). The original trial assessed composite CV death, nonfatal myocardial infarction and nonfatal stroke (MACE). For this investigation, CV outcomes were analyzed by baseline eGFR: <45, 45 to <60, 60 to <90, and ≥90 ml/min/1.73 m^2. When administered to patients with an eGFR <60 ml/min/1.73 m^2, the impact of canagliflozin on HbA1c and body weight was diminished in comparison with those whose eGFR was ≥60 ml/min/1.73 m^2: HbA1c (-0.43 versus 0.64%, p-heterogeneity <0.0001); body weight (-1.16 versus -1.43 kg, p-heterogeneity = 0.0002). In contrast, the impact on blood pressure appeared independent of baseline eGFR < vs. > 60 ml/min/1.73 m^2. Upon evaluation of CV outcomes, the impact of canagliflozin across all levels of renal function was comparable for the majority of measures (Figure 4). However there appears to be a trend towards greater protection from stroke when eGFR is reduced (p=0.01). From this analysis, the investigators concluded that CV protection occurs mostly across different levels of kidney function despite the diminished impact on HbA1c at reduced eGFR.* Similar findings with empagliflozin in EMPA-REG OUTCOME have already been published (Wanner *et al, Circulation* 2018 137:119-129).*

The CANVAS program data were also used to assess the impact of baseline HbA1c values on CV outcomes (abstract 661). This prespecified subgroup analysis conducted by Matthews and international colleagues compared the impact of canagliflozin on CV, mortality, renal, and safety outcomes in patients with baseline HbA1c values <8% (n=4,411) versus those with HbA1c ≥8% (n=5,731). Secondary outcomes such as HbA1c reduction, body weight, systolic blood pressure, and geometric mean change in UACR were assessed as well. There were consistent effects between subgroups with respect to CV and renal outcomes, however, a lower risk of CV death (p=0.01) and all-cause mortality (p=0.005) was

Figure 3. Renal Function Over Time in Patients with Nephrotic-Range Proteinuria in EMPA-REG Outcome



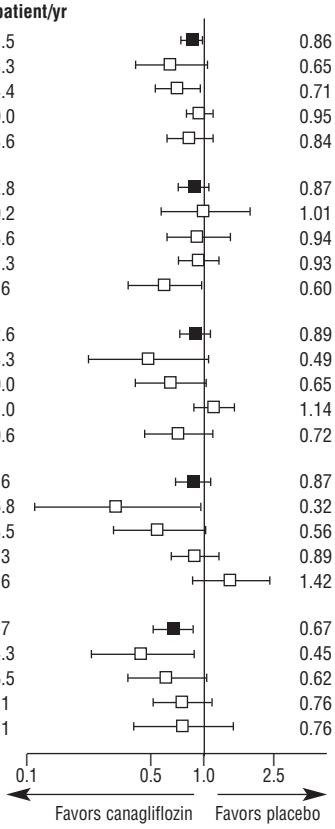
Patients analyzed	Baseline	4	12	28	52	66	80	94	108	122	136	150	164	178	192
Placebo	42	41	40		36	34	32	31	25	19	14	13	12	6	
Empagliflozin	68	67	66		62	58	53	60	49	43	33	28	23	16	

eGFR according to MDRD study formula. Based on a mixed-model, repeated-measures analysis of on-treatment data for patients treated with ≥1 dose of study drug who had a baseline and a ≥1 post-baseline measurement.

eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Real Disease.

Figure 4. Cardiovascular Outcomes in Patients by Baseline eGFR in CANVAS

Outcome	eGFR	Canagliflozin	Placebo	Hazard Ratio (95% CI)	Interaction p-value
		No. events per 1000/patient/yr			
MACE	All	26.9	31.5	0.86 (0.75-0.97)	0.33
	<45	44.7	63.3	0.65 (0.41-1.03)	
	45 - <60	33.2	44.4	0.71 (0.53-0.95)	
	60 - <90	26.8	29.0	0.95 (0.80-1.13)	
	≥90	20.8	23.6	0.84 (0.62-1.13)	
CV death	All	11.6	12.8	0.87 (0.72-1.06)	0.53
	<45	29.5	30.2	1.01 (0.57-1.81)	
	45 - <60	19.4	18.6	0.94 (0.62-1.42)	
	60 - <90	10.7	11.3	0.93 (0.72-1.22)	
	≥90	6.4	9.6	0.60 (0.37-0.97)	
Fatal/non-fatal MI	All	11.2	12.6	0.89 (0.73-1.09)	0.08
	<45	13.6	23.3	0.49 (0.22-1.07)	
	45 - <60	12.8	19.0	0.65 (0.41-1.04)	
	60 - <90	12.1	11.0	1.14 (0.87-1.49)	
	≥90	8.0	10.6	0.72 (0.46-1.13)	
Fatal/non-fatal stroke	All	7.9	9.6	0.87 (0.69-1.09)	0.01
	<45	5.2	16.8	0.32 (0.11-0.96)	
	45 - <60	7.1	13.5	0.56 (0.31-1.00)	
	60 - <90	7.7	9.3	0.89 (0.65-1.21)	
	≥90	9.5	6.6	1.42 (0.86-2.36)	
Hospitalization for heart failure	ALL	5.5	8.7	0.67 (0.52-0.87)	0.62
	<45	16.9	34.3	0.45 (0.23-0.88)	
	45 - <60	9.6	16.5	0.62 (0.37-1.03)	
	60 - <90	4.6	6.1	0.76 (0.52-1.12)	
	≥90	3.7	5.1	0.76 (0.40-1.47)	



CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; MACE=major adverse cardiovascular event.

observed in patients with baseline HbA1c values ≥8%. The investigators suggested this difference may be driven, in part, by the risk of CV death in this subgroup. Safety profiles were comparable regardless of baseline glycemia. With respect to secondary endpoints, the impact on HbA1c and UACR was greater in the baseline HbA1c ≥8% subgroup, whereas there was no difference on body weight and systolic blood pressure. Overall, the investigators concluded that canagliflozin confers benefits on CV and renal outcomes independent of baseline HbA1c, yet any reductions in CV and all-cause mortality seem to occur predominately in those with baseline HbA1c ≥8%.*

An on-going area of research is the utilization of the SGLT inhibitors in the management of Type 1 diabetes (see page 14). Sotagliflozin,* a dual SGLT1 and SGLT2 inhibitor, is currently in development for this indication. SGLT1 inhibition blocks glucose and galactose absorption in the GI tract. Garg and colleagues from the US conducted a double-blind, randomized trial in Type 1 patients (n=793) managed by insulin via multiple daily injections (40%) or pump (60%). Patients received sotagliflozin 400 mg (n=262), sotagliflozin 200 mg (n=263), or placebo (n=268) daily following 6 weeks of insulin optimization (abstract 609). The primary endpoint, HbA1c change from baseline at week 24, was statistically significant for both doses of sotagliflozin versus placebo-corrected change from baseline: 200 mg (-0.36%, p<0.001) and 400 mg (-0.41%, p<0.001). This effect was sustained over 52 weeks. Additional outcomes included: significant reductions in body weight as well as higher proportion of patients achieving a "net clinical benefit" defined as patients with HbA1c <7.0% at week 52 without severe hypoglycemia or DKA after randomization. Overall, sotagliflozin was well tolerated, however, adverse events such as an increase in genital mycotic infections, diarrhea, and episodes of DKA were seen in the treatment arm.

In addition to the risk of DKA, which is well described with the SGLT2 inhibitor class, a potential risk for stroke has been raised with at least empagliflozin. Roddick *et al.*, London, UK conducted a systematic review and meta-analysis to investigate stroke safety for this class (abstract 634). Multiple databases (MEDLINE, Embase and CENTRAL) were searched identifying placebo-controlled trials, phases 2-4, of at least 12 weeks duration in patients with Type 2 diabetes. Outcomes evaluated were any and non-fatal stroke events. The Mantel-Haenzel method was used to complete a random-effects pairwise meta-analysis. Neither stroke safety nor non-fatal stroke was associated with the SGLT2 inhibitors as a class (RR 0.99, 95% CI 0.79-1.23, p=0.92 and RR 1.03, 95% CI 0.86-1.23, p=0.78, respectively). In addition, no individual SGTL-2 inhibitor (i.e., canagliflozin, dapagliflozin, empagliflozin, ipragliflozin) was associated with increased risk for either category. Recognizing the limitations of meta-analyses, the investigators concluded that SGLT2 inhibition does not negatively impact stroke risk in patients with Type 2 diabetes.

This increasingly popular drug class will likely have a prominent position in the new ADA-EASD guidelines—stay tuned for our next edition.

UKPDS: It Never Gets Old

Over forty years since its inception, the United Kingdom Prospective Diabetes Study (UKPDS) program continues to provide direction in the management of patients with diabetes. An entire session at the EASD 2018 annual meeting was dedicated to its past, present and future.

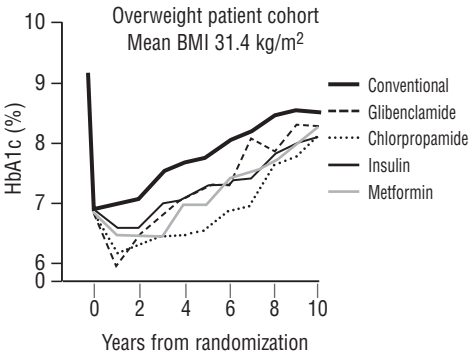
Rury Holman, FRCP, FmedSci, University of Oxford UK, the first speaker, gave a reprise of the trial in his talk titled "UKPDS: The First 40 Years". By way of background, UKPDS, a landmark 20-year, multicenter, randomized, controlled outcome trial of different blood glucose and blood pressure therapies in 5,102 patients with newly diagnosed Type 2 diabetes, was launched in 1977 and completed in 1997 (UKPDS 8, *Diabetologia* 1991;34:877-89). Patients were randomized to conventional glucose control, with the aim of lowest fasting glucose attainable with diet alone, or to intensive glucose control, aiming for fasting glucose <108 mg/dL with monotherapy (i.e., sulfonylurea [n=1573], basal insulin [ultralente or isophane, n=1156], or metformin [if >120% of ideal body weight, n=342]). The design was limited by prevailing regulatory and other constraints at the time, including concerns about the safety of combination therapy, metformin's approval for only overweight patients, and glycemic rescue therapy used only for fasting glucose ≥270 mg/dL or hyperglycemic symptoms. The total burden of disease, including 21 separate fatal and nonfatal endpoints, was assessed by an adjudication committee that stayed for the full study and post-study monitoring.

The first novel finding of UKPDS highlighted by Dr. Holman was that despite enrollment of patients with newly diagnosed diabetes, approximately half of patients already had a diabetes complication. Approximately 1 in 5 had retinopathy, 18% abnormal ECG, 14% ≥2 absent foot pulses ± ischemic feet, and a small percentage CV issues despite the exclusion of patients with a history of a CV event in the year prior to enrollment (3% each angina and intermittent claudication, 2% MI, and 1% stroke or TIA).

Another novel discovery of UKPDS was that hyperglycemia progresses over time almost in a monotonic fashion in Type 2 diabetes, with parallel increase in HbA1c over time, irrespective of the intervention, after an initial decrease during the run-in period (Figure 5). By way of explanation, beta-cell function (assessed by HOMA) was measured and noted to decrease by ~4% per year.

The UKPDS investigators also uncovered the relationship between glucose exposure and risk of diabetes complications. Incidence of microvascular disease increased by 15-fold at the highest levels of HbA1c (vs. 6%) and risk of MI doubled (*BMJ* 2000;321:405-12). Furthermore, diabetes in the context of hypertension was determined to significantly increase the risk of any diabetes-related event (RR=1.45, p<0.0001) (*J Hypertension* 1993;11:309-31). This finding caused the study size to be increased and additional treatment arms added in 1987, randomizing patients to "tight" (captopril or atenolol) versus "less tight" blood pressure control. Subsequently, treatment arms were added including glycemic rescue, with insulin being added for fasting glucose >108 mg/dL on maximum therapy.

Figure 5. Profile of Glycemia Over Time in UKPDS



UKPDS 34. *Lancet* 1998;352:837-53.

The primary results were first reported in 1998 at EASD, Barcelona, with 5 simultaneous publications in *The Lancet* and *BMJ*! Among the more interesting results presented was that a <1% decrease in median HbA1c (i.e., 7% vs. 7.9%) reduced risk over a median 10.7 years follow-up by 12% for the primary endpoint of any diabetes-related event (p=0.029), 25% for microvascular disease (p=0.0099), 21% for retinopathy (p=0.015), 33% for albuminuria (p<0.0001), and 16% for MI (p=0.052) (UKPDS 33. *Lancet* 1998;352:837-53).

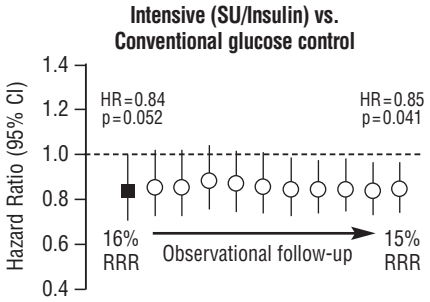
In the metformin substudy (n=342 metformin, n=411 diet), a decrease in median HbA1c of 0.6% was achieved over a median of 10.7 years of follow-up, which resulted in reduced risk by 32% for any diabetes-related event (p=0.0023), 39% for MI (p=0.010), 36% for all-cause mortality (p=0.011), and 29% for microvascular disease (p=0.169) (UKPDS 34. *Lancet* 1998;352:837-53).*

In the blood pressure portion of the trial, a decrease in blood pressure of 10/5 mm Hg (from 154/87 to 144/82) over a median 8 years follow-up resulted in reduced risk by 24% for any diabetes-related event (p=0.0046), 44% for fatal and non-fatal stroke (p=0.013), 37% for microvascular disease (p=0.0092), 34% for retinopathy progression (p=0.0038), and 47% for vision deterioration (p=0.0036) (UKPDS 38. *BMJ* 1998;317:703-13).

Subsequently, the UKPDS Type 2 diabetes risk engine (derived from 53,000 patient-years of data) was launched in 2002 (www.dtu.ox.ac/riskengine). The risk engine uses multiple risk factors to calculate a global risk estimate. In external validation, the risk engine accurately predicted coronary heart disease (CHD) and stroke event rates as observed in other studies (e.g., HPS, CARDS). It can not only illustrate likely effect of therapeutic interventions, but also can be incorporated into clinical database software for automated risk calculations.

Holman then presented data showing the impact of UKPDS findings (advocating tighter glucose control) following their incorporation into treatment guidelines. For instance, according to NHANES data the proportion of Type 2 diabetes patients with HbA1c <7% increased from 37% in 1999-2000 to 57% in 2003-2004 (Hoerger *et al.*, *Diabetes Care* 2008;31:81-6). Diabetes complication rates also decreased in the ~10 years after UKPDS results were published (*N Engl J Med* 2014;370:1514-23) during the time that the benefits of tighter glucose control, blood pressure control (from UKPDS and other studies), and lipid reduction were appreciated.

Figure 6. Legacy Effects of Early Glucose Control—MI



Other findings from UKPDS were the impact of nephropathy on annual risk of death: 1% with no nephropathy, increasing 3-fold in those with microalbuminuria, 5-fold in those with macroalbuminuria, and 19-fold in those with ESRD (UKPDS 64. *Kidney International* 2003;63:225-32). Also, intensive glucose control and tight blood pressure control achieve benefits far greater than either alone, supporting multifactorial interventions (p for tend = 0.024) (UKPDS 75. *Diabetologia* 2006;49:1761-9).

Ten-year post-trial monitoring (treatment no longer being directed by protocol) revealed the "legacy effect" of early glucose control on MI (Figure 6), mirroring "metabolic memory" from the DCCT. The mechanism by which early treatment results in long-lasting benefits is unknown, but current thinking suggests epigenetic variation with DNA methylation.

Holman concluded his talk by summarizing the key impacts of UKPDS: 1) At diagnosis, half of Type 2 diabetes patients had complications, identifying the need to find them earlier. 2) Hyperglycemia is an independent risk factor for CHD. 3) Hyperglycemia is progressive, due to declining beta-cell function. 4) Improved glucose control can substantially reduce the risk of microvascular disease (~25%) and perhaps macrovascular disease (~15%). 5) The glycemic "legacy effect" means that glucose-lowering therapies need to be introduced as early as possible to maximize their benefit. 6) Metformin can substantially reduce CV and all-cause mortality,* supporting it as foundation therapy in treatment guidelines. 7) Hyperglycemia and hypertension are "bad companions" in diabetes. 8) While improved blood pressure control by itself reduces the risk of microvascular disease and stroke, combined with improved glucose control it leads to additive benefits. 9) More effective glucose control can be achieved with earlier introduction of combination therapy. And, 10) Nephropathy is a major risk factor for CVD and premature death.

Professor David Matthews, FRCP, DPhil, Oxford, UK, closed the session with his presentation entitled "Putting the UKPDS into perspective." As a mechanism to provide this perspective, he shared four misconceptions about the UKPDS and debunked each:

(1) Misconception #1: *The results related to intensive glucose control are not to be trusted given that another trial (i.e., ACCORD) demonstrated an increase in death rates upon lowering A1c to normal values.* Matthews meticulously described the differences in trial designs between UKPDS and ACCORD, specifically the initiation of glycemic interventions at diagnosis in patients with no history of a CV event in the former.

(2) Misconception #2: *UKPDS used old-fashioned glucose-lowering techniques that are not relevant today.* He argued that the UKPDS was about glycemic POLICY such as early tighter glucose control and not really about individual drug choices.

(3) Misconception #3: *The metformin arm (n=342) was underpowered – it is uncertain if the result is true.* He suggests that given the patients had to be randomized to metformin, the real "n" was 753. (Plus, we would add, a P-value is a P-value!)

(4) Misconception #4: *Many recent trials of newer agents (e.g. DPP-4 inhibitors show no difference in CV outcomes, therefore, lowering glucose cannot be very important.* Matthews identified that the majority of these were actually safety trials, predicated on glycemic equipoise and not seeking. So, such a comparison is not justified.

He then reminded the audience of the UKPDS' numbered publications (84) along with the countless citations (15,637 for UKPDS 33 alone) and considers its impact on health care synonymous with DCCT (tight glycemic control in Type 1 diabetes), 4S (simvastatin in CHD patients), and the British Doctors' Smoking Study impacting clinical, basic science, and public health.

He left the audience with what he described as the penultimate slide, a quote from Professor Philip Home, Newcastle, UK: "*The UKPDS has evidently been unusually influential in the development of treatment guidelines, clinical education, and the thinking of healthcare professionals. By inference it must be responsible for a significant part of the improvement in health outcomes in people with Type 2 diabetes over the last decade.*"

We cannot possibly provide a better summary statement!

What's New in Type 1 Diabetes?

Stringent glycemic control in patients with Type 1 diabetes is difficult to achieve due to the eventual complete absence of endogenous insulin secretion. Over time, counter-regulatory failure develops, resulting in even greater lability. Superimposed upon this pathophysiology is the natural tendency in some patients to become less diligent with their self-management skills over time. As a result, the maintenance of HbA1c targets becomes more elusive.

Over the past several years, however, there have been enormous advances in insulin pump and continuous glucose sensor technologies, making it easier to reduce HbA1c and glycemic variability. In addition, there has been substantial research into the use of non-insulin therapies as adjuncts in patients with Type 1 diabetes, though to date, the only such drug approved for use in the US is the injectable pramlintide. Several presentations this week caught our attention.

Real-world Use of the Hybrid Closed-Loop Pump

Lee and Medtronic investigators reported on the real-world use of the MiniMed™ 670G system with the SmartGuard™ Auto Mode feature, which automatically adjusts basal insulin delivery through its 'hybrid closed-loop' algorithm (abstract 803). Their study cohort included 1833 Type 1 diabetes patients (mean±SD age was 45.8±16.5, total daily dose of insulin [TDD] 45.3±26.1 units) as well as 58 insulin-dependent Type 2 diabetes patients (age 54.6±9.0 years, TDD 68.7±43.0 units). Eligible patients had at least 3 months of CareLink™ software data (insulin utilization, continuous glucose monitoring [CGM], etc.). Glycemic control during baseline Manual Mode (i.e. traditional patient-operated pump) was compared to that after Auto Mode was enabled (i.e., into hybrid closed-loop) and evaluated by diabetes type. Change from baseline data were analyzed using a paired t-test or Wilcoxon signed-rank test.

Use of the MiniMed™ 670G system was associated with a significant increase in time in target glucose range (70-180 mg/dl) and a significant reduction in serum glucose values in hyperglycemic ranges (>180, >250 and >350 mg/dl; Table 4) without any associated increase in hypoglycemia. These findings suggest that the advantages of automated basal insulin delivery with the MiniMed™ 670G system as documented in clinical trials also translates to real-world use.

Table 4. Percentage of Glucose Values Across Sensor Glucose Ranges

	Patients with Type 1 Diabetes n = 1833			*Patients with Type 2 Diabetes n = 58*		
Sensor Glucose Range (mg/dL)	*Manual Mode (Baseline)*	*Auto Mode*	*p-value*	*Manual Mode (Baseline)*	*Auto Mode*	*p-value*
<50	0.22±0.38	0.19±0.29	0.050†	0.09±0.20	0.08±0.14	0.219†
<54	0.40±0.62	0.35±0.47	0.978†	0.16±0.32	0.16±0.25	0.175†
<70	2.19±2.27	1.88±1.68	<0.001†	1.23±1.85	1.03±1.12	0.508†
70 ≤ SG ≤ 180	65.25±14.78	73.47±9.40	<0.001†	70.74±17.35	76.44±11.06	<0.001
>180	32.56±15.52	24.65±9.58	<0.001†	28.03±17.55	22.53±10.78	<0.001
>250	8.17±7.64	5.13±4.41	<0.001†	6.20±7.88	4.27±4.61	0.015†
> 350	0.50±0.98	0.29±0.57	<0.001†	0.45±1.06	0.24±0.64	0.099†

Data presented as mean (SD).
† By Wilcoxon signed-rank test.

Eversense CGM Use for Six Months by Adolescents

Abitbol and investigators from North America presented the results of a prospective, single-center study of Eversense® XL (Senseonics, Maryland USA), an implantable CGM system, in which safety and accuracy through 180 days of sensor wear was observed in a primarily adolescent population with Type 1 diabetes (abstract 86). CGM system accuracy studies were performed every 30 days.

Thirty-six participants (23 male, mean age 17 ± 9.2 years, mean BMI 22 ± 4 kg/m^2) received the CGM system, with 1 withdrawing on the first day 1 due to IV access issues. Overall, mean absolute relative difference (MARD) was 9.4% (95% CI: 8.6%-10.5%). CGM system agreement with the gold-standard Yellow Springs Instrument (YSI) blood glucose values within 15 mg/dl or 15% of YSI glucose values (n=7163) through 60, 120, and 180 days was 82.9%, 83.6% and 83.4% (95% CI: 79.7%-85.5%), respectively. Clarke Error Grid analysis showed 99% of paired (CGM and reference YSI glucose analyzer) values in the clinically acceptable error zones A and B. No insertion/removal or device-related serious adverse events were reported in the 180 days post-insertion.

SGLT2 Inhibitor Therapy in Type 1 Diabetes

Currently approved for use only in Type 2 diabetes, SGLT2 inhibitors are an attractive add-on therapy to insulin in patients with Type 1 diabetes.* Preliminary studies have shown that these glucosuric agents can improve HbA1c, decreased insulin requirements, and lead to modest weight loss in this setting. However, the development of diabetic ketoacidosis (DKA) as a potential adverse effect has curbed enthusiasm for this indication. The DKA in treated patients can be euglycemic in nature and therefore more difficult to identify.

Evidence for the potential benefits of SGLT2 inhibitor when added to insulin for Type 1 diabetes was presented at a symposium entitled, "Empagliflozin as an Adjunct to Insulin in Type 1 Diabetes".* Julio Rosenstock, MD, University of Texas, Southwestern Medical Center, Dallas, TX, and Bruce Perkins, MD, MPH, University of Toronto, presented efficacy and safety results, respectively, from the two randomized, placebo-controlled trials in the EASE Phase 3 program, investigating the use of empagliflozin as an adjunct to intensified insulin in adults with Type 1 diabetes for ≥12 months treated with multiple daily injections or using an insulin pump. Other selection criteria were eGFR ≥30, inadequately controlled glycemia after lead-in 6-week insulin intensification (HbA1c 7.5-10.0%), and no severe hypoglycemia or DKA in the 3 months before randomization.

In a Phase 2 study, EASE-1, 2.5 mg of empagliflozin had a similar effect on urine glucose excretion (UGE) in Type 1 diabetes patients as the higher doses (10, 25 mg) in Type 2 diabetes. This led to a small but significant decrease in HbA1c (placebo-corrected HbA1c -0.35%, $p<0.05$) and a small amount of weight loss (-1.5

kg, p<0.001) at day 28 (Pieber *et al., Diabetes Obes Metab* 2015;17:928-35).

In the Phase 3 EASE-2 (n=730) and EASE-3 (n=975) studies (mean age 44, BMI 28, 51% female, 94% white) the primary efficacy endpoint, placebo-corrected change from baseline in HbA1C after 26 weeks of treatment, was met in both trials for all investigated doses of empagliflozin (Table 5).

Total daily insulin dose was significantly (<0.0001) decreased from baseline to week 26 in all treatment arms (EASE-2: by 13% with both doses; EASE-3: 6%, 10%, and 13% with 2.5 mg, 10 mg, and 25 mg, respectively).

In pooled analysis of data from the phase 3 EASE studies, there was a 2-3 fold increased risk of DKA with empagliflozin 10 mg and 25 mg vs. placebo. The DKA risk correlated with concomitant illness or inadequate insulin administration (e.g., pump failure); the risk appeared to be higher in females and with insulin pump use. The incidence of DKA with the 2.5 mg dose, however, was similar to that with placebo (1.62 vs. 2.52 per 100-patient years) in the EASE-3 trial, with all cases classified as mild.

Empagliflozin did not increase the rate of investigator-reported reports of hypoglycemia, including severe events, despite the modestly reduced HbA1c.

We found these data potentially attractive for our difficult to control Type 1 diabetic patients, but it's not clear if a 0.3% reduction in HbA1c and a 6% reduction in insulin dose with the apparently safe 2.5 mg dose will pass muster at the FDA. Of course, it is not known whether the CV or the renal benefits demonstrated with this drug in Type 2 diabetes might carry over to Type 1 patients.

Table 5. HbA1c Reduction from Baseline at Week 26 in Empagliflozin EASE Trials

Study	*Dose*	*Mean Change vs. Placebo*	*95% CI*	*p value*
EASE-2	10 mg	-0.54%	-0.65%, -0.42%	<0.0001
	25 mg	-0.53%	-0.65%, -0.42%	<0.0001
EASE-3	2.5 mg	-0.28%	-0.42%, -0.15%	<0.0001
	10 mg	-0.45%	-0.58%, -0.32%	<0.0001
	25 mg	-0.52%	-0.66%, -0.39%	<0.0001

Insulin Treatment of LADA

With the aim of better understanding the optimal beta-cell preserving treatment for latent autoimmune diabetes (LADA) (i.e., treat with insulin as in Type 1 diabetes or with oral agents as for Type 2 diabetes?) Hals and coworkers from Norway and Sweden randomized 61 GAD antibody (A)-positive patients (age 30-75 years [median, 53 years], mean BMI 27 kg/m^2, duration of diabetes <3 years, and no need for insulin) to metformin plus either insulin or the DPP-4 inhibitor sitagliptin* (abstract 246). Participants were stratified by age, BMI, and degree of GADA positivity. Beta cell function was evaluated by C-peptide, insulin, and proinsulin recorded during glucagon stimulation performed 3, 9, and 21 months after randomization (and always after 48-hour temporary withdrawal of study medication).

HbA1c was similar at baseline and after 21 months of intervention (median 6.8% and 6.6%, respectively, in the insulin arm and 6.5% and 6.6%, respectively, in the sitagliptin arm). Stimulated C-peptide after 21 months decreased similarly in both groups (medians, insulin: -0.09, sitagliptin: -0.08 nmol/L). Stimulated insulin was unaltered at 21 months of insulin treatment (median 24.5 µU/ml at randomization, 24.1 µU/ml at 21 months), whereas levels decreased following treatment with sitagliptin (from 22.4 to 15.2 µU/ml, p<0.03 vs. insulin). The ratio of proinsulin/insulin (a marker of beta-cell stress) did not change following insulin treatment (median 0.13 at randomization, 0.11 at 21 months) but increased following sitagliptin (0.13 and 0.21, respectively; p<0.02 vs. insulin). The investigators also assessed the effects of apparent autoimmunity in the whole study population after dichotomizing by titers (low/high) of GADA. Stimulated C-peptide did not change from randomization to 21 months in low-GADA (median 0.77 and 0.78, respectively) but decreased in high-GADA participants by 27% (from 0.87 to 0.60 nmol/l, p<0.05 vs. low GADA). Reciprocally, the proinsulin/insulin ratio increased from 0.13 to 0.21 in high-GADA but was unaffected with low-GADA participants (from 0.14 to 0.15, p<0.04 for difference high vs. low GADA). Further analysis did not detect a modulating effect by insulin treatment on these parameters. Taken together, these results suggest that early insulin treatment may be advantageous in LADA but does not protect against autoimmunity-induced adverse effects on beta cells and resulting decline in insulin release. We note the equivalent HbA1c in both groups at the end of the trial, however.

CVD Mortality

Age at diagnosis is an extremely important complication and mortality risk marker in Type 1 diabetes.

On the initial day of the EASD congress, Sattar and associates from Sweden reported results of the first study to examine how age at diabetes diagnosis relates to excess risk of death and CV outcomes, while accounting for duration of diabetes (abstract 47). They estimated the excess risk of all-cause mortality, CV mortality, non-CV mortality, acute myocardial infarction, stroke, cardiovascular disease (composite of AMI and stroke), coronary heart disease, heart failure, and atrial fibrillation in individuals with Type 1 diabetes compared to matched controls from the general population. Participants were categorized into five groups, according to age at diagnosis: 0 to 10 years, 11 to 15 years, 16 to 20 years, 21 to 25 years, and 26 to 30 years. Analyses were performed using Cox regression, with adjustment for socioeconomic, demographic variables, comorbidities, and duration of diabetes.

The study cohort included 27,195 persons with Type 1 diabetes and 135,178 matched controls. Over a median follow-up period of 5.1 years, 924 patients with Type 1 diabetes and 1,405 controls died. The investigators reported a remarkable association between age at Type 1 diabetes onset and excess risk of death and all CV outcomes. Early onset Type 1 diabetes was associated with up to 30-fold increased risk of serious CV outcomes. With the exception of atrial fibrillation, no hazard ratio fell below 2.0. Risk of non-CV mortality was also greatest among those with early onset of Type 1 diabetes. Considering risk factor control, increasing age at diagnosis was associated with better glycemic control, higher blood pressure, higher prevalence of smoking, more physical activity, and higher socioeconomic status.

These data suggest that age at onset of Type 1 diabetes is a fundamental predictor of survival, as well as all CV outcomes, with the exception of atrial fibrillation.

More research is needed into optimal treatment strategies for our patients with Type 1 diabetes to help them attain desired glycemic control and avoid long-term complications, including mortality.

So Many Posters, So Little Time....

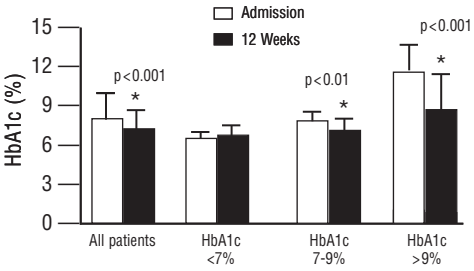
Inpatient Use of Linagliptin

Umpierrez and American investigators randomized (non-cardiac) surgical patients with Type 2 diabetes (blood glucose [BG] 140-400 mg/dl), treated with diet, oral agents, or insulin (total daily dose [TDD] ≤0.5 units/kg) to either linagliptin 5 mg daily (n=129) or a basal-bolus insulin regimen (n=122) (abstract 769). Insulin-treated patients were started at a TDD of 0.4 or 0.5 U/kg/day for randomization BG between 140-200 mg/dl or >200-400 mg/dl, respectively. TDD was reduced by 50% for those with GFR <45 ml/min/1.73m^2. Both groups received correction doses of rapid-acting insulin for BG >140 mg/dl before meals, or every 6 hours if NPO. 221 patients from the inpatient study were also treated according to a discharge algorithm based on admission HbA1c: linagliptin or preadmission oral agents if <7%, and linagliptin with glargine at 50% or 80% of the hospital daily dose if 7%-9% and >9%, respectively.

Mean daily inpatient BG was higher in the linagliptin group (171 vs. 159 mg/dl, p=0.04). Linagliptin resulted in similar improvement in glycemic control compared to basal-bolus insulin (mean daily inpatient BG 159 vs. 154 mg/dl) in patients with a randomization BG <200 mg/dl (observed in 63% of the overall cohort). However, basal-bolus insulin regimen was superior to linagliptin in patients with randomization BG ≥200 mg/dl (mean daily inpatient BG 165 vs. 196 mg/dl, p<0.001). Linagliptin resulted in fewer hypoglycemic events (1.6% vs.11%, p=0.001, relative risk reduction of 86%) and a lower number of daily insulin injections (2±3 vs. 3±3, p<0.001) compared to basal-bolus. There were no differences in length of hospital stay or in the rate of perioperative complications between treatment groups. The proposed HbA1c-based hospital discharge algorithm, including linagliptin with or without basal insulin, resulted in efficacious glycemic control after discharge, especially in patients with an admission of 7-9% and >9% (Figure 7).

Umpierrez' data suggests that in selected hospitalized patients with mild hyperglycemia, the much simpler to use DPP-4 inhibitor may be as good as the more complex insulin strategies that are now fashionable. The impact on other clinical outcomes in this group is uncertain. A larger multicenter trial will be needed before such a strategy is widely implemented. Of course, insulin is clearly needed for those with blood glucose in excess of 200 mg/dl.

Figure 7. Change in HbA1c from Admission to 3 Months Post-Discharge



Testosterone in Hypogonadal Men with Type 2 Diabetes

Numerous experimental and clinical studies have shown beneficial effects of testosterone in hypogonadal men with Type 2 diabetes. In an ongoing observational registry study, Wissinger and coworkers from Germany and the US identified 481 men with Type 2 diabetes and hypogonadism (total testosterone ≤12.1 nmol/L); 311 elected to be treated with testosterone undecanoate (TU) injections 1000 mg every 12 weeks (T-group) and 170 did not, serving as controls (abstract 675). Mean age was 61.8±5.3 years [T-group] and 63.5±4.9 years (control group).

Fasting glucose decreased from 139±22 to 95±2 mg/dl at 10 years in the T-group with statistical significance vs. the previous year for the first 2 years, and increased from 113±13 to 148±49 mg/dl in the control group. The estimated adjusted difference between groups was -6.2% (p<0.0001 for all).

At baseline, 61 patients in the T-group were on insulin (mean dose 34±11.1 units/day), as were 63 in the control group (mean dose 30.7±6 units/day). The mean dose requirement in the T-group declined to 19.9±10.5 units/day, with statistical significance vs. previous year for the first 8 years. In the control group, insulin dose increased to 42.2±8.5 units/day, with statistical significance vs. previous year for the entire observation time. The estimated adjusted difference between groups was -33.1 units/day (p<0.0001 for all).

In the T-group, 113 men (80.1%) achieved HbA1c <6.5% and 128 (90.8%) achieved HbA1c <7.0% at the last measurement.

In the T-group, weight decreased from 113.4±13.9 to 90.7±8.6 kg at 10 years (p<0.0001), with statistical significance vs. previous year for the first 9 years. Waist circumference decreased from 112.6±10.7 to 99.6±5.2 cm (p<0.0001), with statistical significance vs. previous year for the first 9 years. In the control group, weight and waist circumference remained stable.

The authors concluded that testosterone treatment of hypogonadism in men with diabetes improves their metabolic control.* Of course, an uncontrolled study like this can only be considered preliminary.

Plantar Pressure-Sensing "Smart Insoles"

Abbott *et al.* from the UK tested the efficacy of a novel plantar pressure-sensing smart insole system, the SurroSense Rx® in reducing diabetic foot ulcer occurrence in high-risk patients (abstract 7). This system comprises pressure-sensing inserts worn inside footwear, recording continuous plantar pressure at 8 sensor locations. When critical pressure thresholds are detected, an alert from a smartwatch encourages alteration in activities to relieve unsafe pressures and prevent ulcers.

58 patients with recent history of, but no active, diabetic foot ulcer, peripheral neuropathy, and absence of peripheral vascular disease were set up with the devices and randomized to either receive feedback alerts (intervention group), or not (control group), from the smartwatch when plantar pressures were 'high'. Participants received device training (including procedures to decrease pressure offloading) and a detailed foot check at baseline and were seen monthly thereafter for a foot check and system calibration. Follow-up was for 18 months or until an ulcer occurred.

Characteristics of the control group (n=26) and intervention group (n=32), respectively, were: mean (SD) age, 67.1 (9.6) vs. 59.1 (8.5) years; Type 1 diabetes, n=4 (15.4%) vs. n=9 (28.1%); and median (range) HbA1c, 7.5% (5.9-9.7%) vs. 8.1% (5.6-13.3%). Self-reported hours of wearing the device were 4.6 (2.9) and 5.1 (3.0) hours/day in the control and intervention groups, respectively (p=0.63).

At follow-up, there were 10 ulcers from 8,638 person-days in the control group and 4 ulcers from 11,835 person-days in intervention group. According to Poisson regression model, the intervention resulted in a 71% reduction in ulcer incidence as compared to control (Incidence Rate Ratio=0.29 [95% CI: 0.09-0.93]; p=0.037). Kaplan-Meier analysis and log-rank test showed no significant between-group difference in time to ulceration (18 month ulcer-free proportion: control -68.4%, intervention -77.5%; p=0.30).

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

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Diabetes**2018**

From the 54th Annual Meeting of the European Association for the Study of Diabetes ■ Berlin, Germany

2015 2016 2017 **2018** 2019 2020 2021

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2018 ADA-EASD Guidelines Unveiled

The glucose-lowering pharmacopeia for T2DM has become increasingly complex over the past two decades. There are now 12 individual drug classes available, most with several members, and many drugs are now available in fixed-dose combinations. Diabetes is a progressive disease with multiple drugs often necessary to adequately control blood glucose concentrations; many patients eventually require insulin injections, sometimes administered several times per day. Since the vast majority of patients with T2DM are treated in general practices and not by specialists, primary care clinicians often seek out guidelines from authoritative sources to assist them in disease management.

Such guidelines from the *American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)* date back to 2006 (Nathan *et al., Diabetes Care* 2006). That set of recommendations advised initial therapy with lifestyle changes and metformin. If additional glucose-lowering was needed to achieve the HbA1c target of <7%, the next step comprised three options: a sulfonylurea, a TZD, or basal insulin. If triple therapy was needed, options not already used as second line would be added (e.g., metformin + sulfonylurea + TZD). Some patients would eventually transition to multiple daily injections of insulin. An updated set of guidelines in 2008 (Nathan *et al., Diabetes Care* 2008) incorporated the new drug category at that time, GLP-1 receptor agonists (GLP-1 RA). That somewhat controversial algorithm categorized the choice after metformin to agents that were 'well-validated' (a sulfonylurea or basal insulin) and those that were 'less well-validated' (pioglitazone or a GLP-1 RA).

In 2012, the ADA-EASD published their first 'Position statement' on this topic (Inzucchi *et al, Diabetes Care* 2012). In contrast to prior consensus guidelines, the statement incorporated external expert review and was formally endorsed by the professional practice committees of both organizations. The emphasis was on patient-centered care, and there were two major sections, the first devoted to glycemic targets and how they might be determined for each patient. The document spelled out the patient and disease characteristics that might influence the intensiveness of treatment efforts, such as risk of hypoglycemia, life expectancy, and comorbidities.

The second section addressed treatment strategies. Metformin remained first-line therapy. Beyond metformin, however, one of six additional drug classes was considered (sulfonylureas, TZDs, dipeptidyl peptidase 4 [DPP-4] inhibitors, GLP-1 RAs, or basal insulin). Given the paucity of data from comparative efficacy trials examining clinical outcomes beyond glycemia at the time, the exact choice for an individual patient would be based on several factors. Potential adverse effects were key considerations: weight gain, hypoglycemia, edema, and gastrointestinal toxicities. The Position Statement stressed treatment personalization. An update was published in 2015 (Inzucchi *et al., Diabetes Care* 2015) to include the newest class at that time, the sodium-glucose cotransporter 2 inhibitors (SGLT2-i). These were given equivalent status to the other five second-line therapies. While the 2012 and 2015 statements were well-regarded and highly cited, many felt that those algorithms were not prescriptive enough—that they left too much choice to the clinician. Yet, they simply reflected the inadequate evidence basis at the time: most drugs were roughly equivalent in terms of glucose-lowering potency, and information related to their long-term CV benefits were lacking. So, the precise choice of drugs after metformin could only weigh the relative risks and benefits of each category, while taking into account the patient's preferences, needs, and values.

Since 2015, however, several clinical trials (EMPA-REG OUTCOME, CANVAS, LEADER, SUSTAIN-6) have demonstrated clear CV benefits of specific glucose-lowering drugs within the SGLT2-i (empagliflozin, canagliflozin*) and GLP-1 RA (liraglutide, semaglutide*) classes. So, in its annually released *Standards of Medical Care*, the ADA has modified the 2015 algorithm to include

increasingly strong recommendations to favor these classes (after metformin) in those patients with established cardiovascular disease (CVD) (ADA. *Diabetes Care* 2018;41:S73-S85).

The long-anticipated updated 2018 ADA-EASD guidelines were presented by its writing committee, led by Dr. John Buse of the University of North Carolina and Dr. Melanie Davies of the University of Leicester, UK on Friday morning to a packed audience at this week's EASD meeting in Berlin. The document was simultaneously released on-line on the websites of the sponsoring organizations. It is now referred to as a 'Consensus Report' but still serves as an official document, fully endorsed by both the ADA and EASD. A draft was presented in Orlando, FL at the ADA's Scientific Sessions in June (see *Diabetes 2018*, volume 37, issue 3). After a period of expert review and public commentary, the document was finalized over the summer.

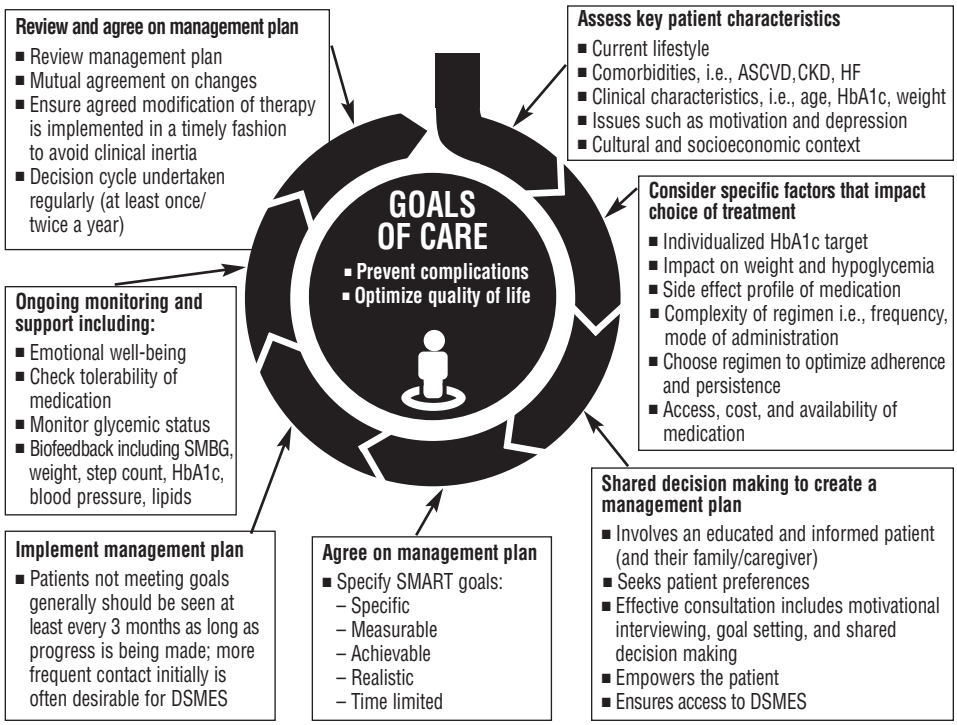
The guidelines are similar to prior versions in that they begin with lifestyle and metformin, with additional therapies added sequentially to achieve the desired HbA1c target. One new element is seen in Figure 8, entitled "*Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes*." This is a flow chart of sorts, outlining the overriding elements of decision-making in the management of hyperglycemia (e.g., assessing patient characteristics, using shared-decision making, selecting and implementing a strategy, etc.).

There are several other important departures from prior guidelines. First, as suggested by the more recent *Standards*, there is now a clear decision node after metformin monotherapy as regards to the presence or absence of CVD. If atherosclerotic CVD (i.e., coronary, cerebrovascular, or peripheral arterial disease) predominates, either an SGLT2-i or a GLP-1 RA is the preferred next choice—preferably a specific drug shown to improve outcomes in large CV outcome trials. If heart failure predominates, however, then an SGLT2-i would be preferred. The same applies for the coexistance of CKD, as long as sufficient renal function exists to allow use of SGLT2 inhibitor therapy. This is a major departure from the 2015 position statement and an evolution from the most recent *Standards* (January 2018).

Another major change is that, for the first time, the guidelines recommend that the first injectable to be used in most patients is a GLP-1 RA and no longer insulin. This recommendation is based on multiple trials showing equivalent glucose-lowering to insulin with less hypoglycemia, and weight loss instead of weight gain.

The Consensus Report also addresses the escalating costs of diabetes medications more so than earlier guidelines and provides specific advice when cost effective care is paramount, utilizing sulfonylureas, pioglitazone, and, when needed, human insulins.

Figure 8. Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



ASCVD=atherosclerotic cardiovascular disease, CKD=chronic kidney disease, HF=heart failure, DSMES=diabetes self-management education and support, SMBG=self-monitored blood pressure

See Figure 9 for the main algorithm from the new report. For an on-line copy of the Consensus Report, go to: http://care.diabetesjournals.org/content/early/2018/09/27/dci18-0033

We feel that the writing committee has done a formidable job in incorporating new and emerging data into a solid set of user-friendly guidelines, which are clearly more evidence-based than those which came before.

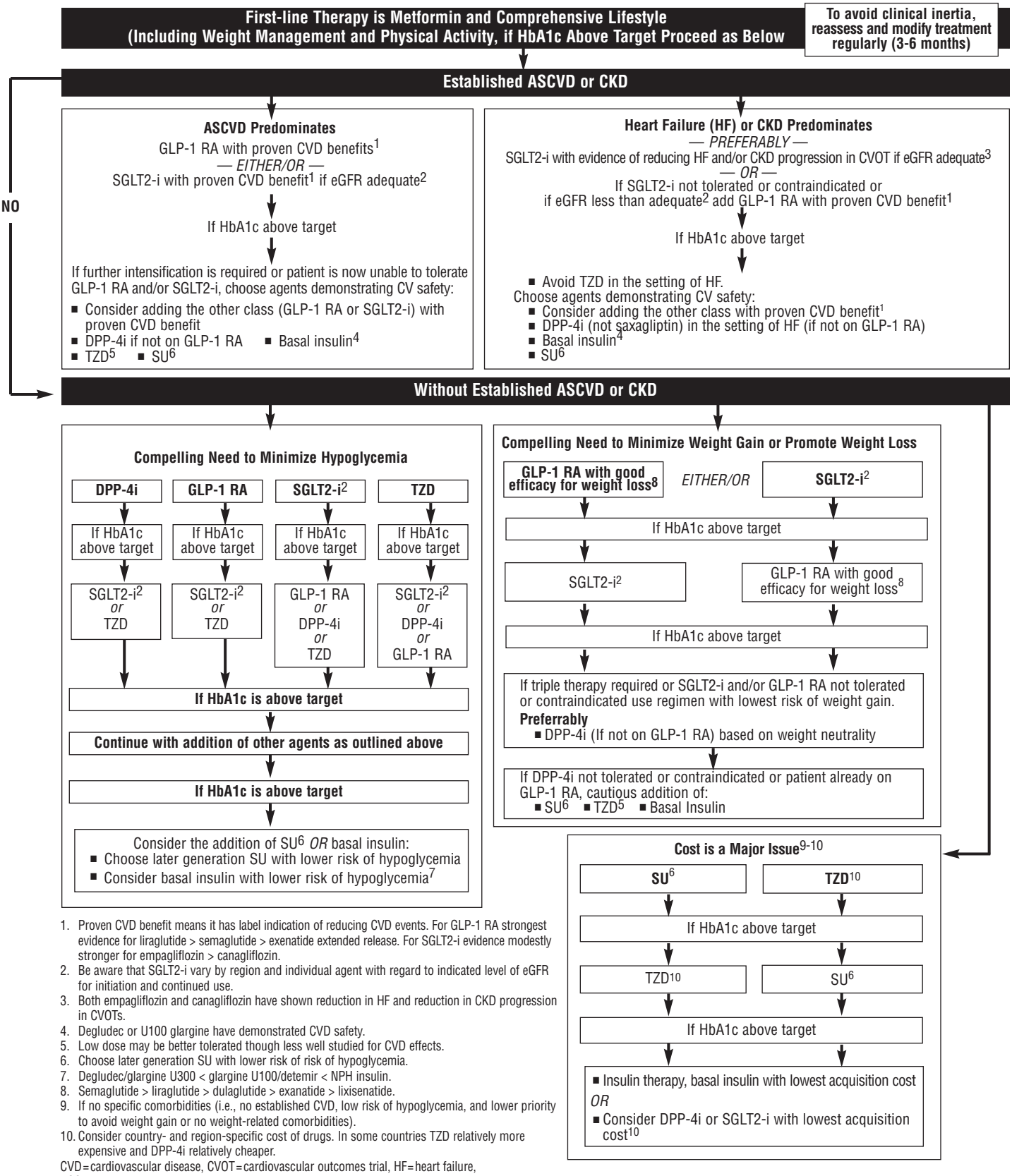
We have only two criticisms. The first is that the authors propose the use of a GLP-1 RA after an SGLT2-i (or in lieu of, if the latter cannot be used) in heart failure patients. Actually, there is no evidence from any GLP-1 RA CV outcome trial that these drugs improve heart failure outcomes. In fact, in two smaller studies (FIGHT, LIVE), the trend was in the opposite direction.

Our second criticism concerns the TZD, pioglitazone. While it is still included in the algorithm, the drug appears to be relegated to a minor role. Yet it has been demonstrated to reduce atherosclerotic events* in both diabetic patients with overt macrovascular disease (PROactive) and in insulin-resistant non-diabetic patients with recent stroke (IRIS). While the drug certainly has side effects (weight gain, edema, heart failure, bone fractures), it can be used safely at lower doses and with close clinical follow-up. Indeed, a recent follow-up paper from IRIS (Young *et al., Circulation* 2018 doi: 10.1161/CIRCULATIONAHA.118.034763) reported no increase in heart failure hospitalizations. This was likely the result of excluding patients with heart failure at baseline and allowing dose adjustments during the trial for weight gain/edema. We believe that this drug, now generically available, still has a role in T2DM patients with CVD who have normal left ventricular function.

One final observation is that the new guidelines continue to be more or less 'glucocentric' insofar as the addition of drugs after metformin is still largely predicated on the need for additional glucose lowering. It would have been interesting to push the envelope a bit more and consider using the newer agents after (or even instead of) metformin irrespective of HbA1c, as suggested by some recent post-hoc analyses from the trials. Of course, firm recommendations along these lines would require clear evidence from other trials.

Irrespective of these minor shortcomings, we anticipate that the new guidelines will be as widely cited as prior ADA-EASD algorithms and will serve the needs of primary care clinicians for years to come.

Figure 9. Glucose-lowering Medication in Type 2 Diabetes: Overall Approach



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2-i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs.
4. Degludec or U100 glargine have demonstrated CVD safety.
5. Low dose may be better tolerated though less well studied for CVD effects.
6. Choose later generation SU with lower risk of risk of hypoglycemia.
7. Degludec/glargine U300 < glargine U100/detemir < NPH insulin.
8. Semaglutide > liraglutide > dulaglutide > exanatide > lixisenatide.
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities).
10. Consider country- and region-specific cost of drugs. In some countries TZD relatively more expensive and DPP-4i relatively cheaper.

CVD=cardiovascular disease, CVOT=cardiovascular outcomes trial, HF=heart failure, ASCVD=atherosclerotic cardiovascular disease.

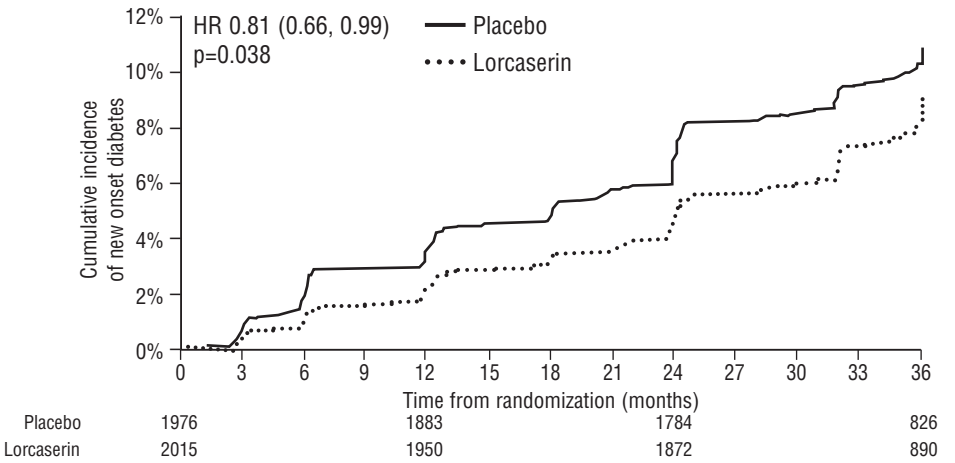
Diabetes Prevention with Lorcaserin: The CAMELLIA Study

Lorcaserin, a selective serotonin 2C receptor agonist that suppresses appetite, was recently shown to reduce body weight without any increase in CV risk (including valvular disease) in overweight/obese patients at high CV risk in the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients trial (CAMELLIA-TIMI 61) (Bohula *et al. N Engl J Med* 2018;379:1107-17). This was noteworthy because several previous weight loss drugs were removed from the market due to increased CV complications, either atherosclerotic events or valvulopathies. While the amount of weight loss in the trial was modest (2.8 kg vs. placebo at 1 year), lorcaserin-treated patients were more than 3 times more likely to have lost at least 5% of body weight at this time point than those assigned to placebo (38.7% vs. 17.4%) (odds ratio, 3.01; 95% CI, 2.74 to 3.30; p<0.001). The drug was also associated with small improvements in blood pressure, lipids, and HbA1c.

In Berlin this week, CAMELLIA's other co-primary outcome, the incidence of diabetes in participants with pre-diabetes at baseline, was presented by Drs. Erin Bohula and Ben Scirica from the TIMI group at the Brigham & Women's Hospital in Boston.

In this large, multinational trial, 12,000 patients with BMI ≥27kg/m^2 with either established atherosclerotic CV disease or multiple CV risk factors were randomized (1:1) to lorcaserin or placebo and followed for a mean of 3.3 years. Routine lifestyle recommendations were provided to all patients. The pre-specified primary metabolic efficacy outcome was incident diabetes assessed in patients with pre-diabetes, i.e. who had either a HbA1c 5.7-6.4% and/or fasting plasma glucose (FPG) 100-125 mg/dl at baseline. The diabetes outcome was defined as a HbA1c ≥6.5% and/or FPG ≥126 mg/dl, either confirmed on a separate occasion or treated with glucose-lowering medications. Pre-specified secondary endpoints were the attainment of normoglycemia (HbA1c <5.7%) in those with pre-diabetes and the remission of hyperglycemia (HbA1c <6.5%) in those with diabetes at baseline, both without the use of any glucose-lowering agents.

Figure 10. Incidence of Diabetes in Overweight/Obese Patients with Pre-diabetes in CAMELLIA-TIMI 61



At baseline, the mean age was 64 years, weight 102 kg, and BMI 35 kg/m^2. 64% of participants were men. 75% had established CVD and 25% solely risk factors. 57% had diabetes, 33% pre-diabetes, and 10% were normoglycemic. These groups experienced 2.6, 2.8, and 3.3 kg weight loss, respectively, vs. placebo (all, p<0.0001).

Over the course of the trial, the incidence of diabetes was reduced by 19%* in the group randomized to lorcaserin (8.5% vs. 10.3%; HR 0.81; 95% CI, 0.66-0.99; p=0.038) (Figure 10). The investigators also found a trend towards the achievement of normoglycemia in the pre-diabetes group* (9.2% vs. 7.6%; HR 1.20, 0.97-1.49; p=0.093). Finally, there was also more frequent remission of hyperglycemia in the diabetes cohort* (7.1% vs. 6.0%; HR 1.21, 1.00-1.45; p=0.049).

The only negative was that in patients with diabetes, severe hypoglycemia, though rare, was more common with lorcaserin (12 vs. 4 events, p=0.054).

How does lorcaserin compare with other weight loss drugs that don't have any intrinsic glucose-lowering action in terms of diabetes prevention? The intestinal lipase inhibitor, orlistat, was associated with a 37% reduction in the XENDOS trial (3305 obese patients over 4 years). Treatment with the appetite suppressant combination, phentermine/topiramate extended release, led to 70-79% risk reductions in the CONQUER/SEQUEL trial (475 patients with BMI ≥27 kg/m^2 and prediabetes or metabolic syndrome over 2 years). So, the effects of lorcaserin appear more modest, but CAMELLIA is still an important trial because it is the first to demonstrate sustained weight loss with definitive CV safety in overweight/obese patients at high CV risk, three-quarters of whom actually had overt CVD.

A Decade of GLP-1-Based Therapy

The GLP-1 RAs, injectable glucose-lowering agents, have now been available for more than a decade. Their role in the management of Type 2 diabetes continues to evolve, with newer strategies, compounds, and delivery methods being studied.

Semaglutide, currently commercially available as a once-weekly, subcutaneously administered GLP-1 RA, is in late stage development as an oral formulation* (dosed daily) for Type 2 diabetes. The results of PIONEER 1, a phase 3a trial with oral semaglutide, were presented by Haluzik and international colleagues (abstract 38). In this randomized, double-blind, placebo-controlled trial, semaglutide 3, 7, or 14 mg daily was assessed in drug naïve uncontrolled Type 2 diabetes patients (n=703) with the primary endpoint being the change from baseline HbA1c at week 26. Secondary endpoints included impact on body weight, safety, and tolerability. Baseline characteristics were comparable between groups including HbA1c and body weight ranging from 7.9-8.0% and 86.9-89.0 kg, respectively. The presenter reported that the treatment difference in HbA1c between

each dose and placebo for randomized patients that remained on study drug, excluding effect of rescue medications, was statistically significant (3 mg: -0.7 [-0.9, -0.5], 7 mg: -1.2 [-1.5, -1.0], and 14 mg: -1.4 [-1.7, -1.2]; $p<0.001$ for all). Change in body weight also reflected dose-dependent changes with statistically significant reductions for the 7 and 14 mg doses ($p<0.05$ and <0.001, respectively). The overall number of adverse events was similar between groups with slightly more GI related side effects with the highest semaglutide dose, which tended to decrease over time. This is the first phase 3 study to demonstrate efficacy and safety for the only orally administered GLP-1 RA.

Research with the subcutaneous formulation of semaglutide through the phase 3 clinical trial program, SUSTAIN, was conducted via a meta-analysis examining efficacy and safety by baseline diabetes duration in the SUSTAIN 1-5 and 7 trials (abstract 740). Madsbad and co-researchers from Europe and the US analyzed efficacy and safety data from 3066 patients, segregating groups by diabetes duration ≤5 years, >5 to ≤10 years, and >10 years. The proportion of patients achieving target HbA1c (<7.0%) (0.5 mg dose: 71%, 66%, and 66%; and 1.0 mg dose: 80%, 79%, and 74% in the three diabetes duration subgroups, respectively) and experiencing ≥5% weight loss (0.5 mg dose: 42%, 39%, and 44%; and 1.0 mg dose: 54%, 56%, and 60%, respectively) was consistent across all diabetes duration subgroups. Similarly, the proportion of patients reporting adverse events was comparable among subgroups.

Subgroup analyses from the LEADER CV outcomes trial that previously demonstrated a reduction in risk of major CV events with daily liraglutide versus placebo in patients with Type 2 diabetes and high risk for CV events continue. Poulter *et al.* compared the effect of liraglutide versus placebo on CV outcomes in patients with CKD at baseline (abstract 74). The CKD subgroups were divided by eGFR (<60 or ≥60 ml/min/1.73 m^2) or albuminuria (micro/macroalbuminuria ≥30 mg/g creatinine) or normoalbuminuria (<30 mg/g creatinine). The *post hoc* analysis demonstrated a significant reduction in diverse CV events and mortality versus placebo in patients with and without CKD.* The complete summary is available in *Circulation* 2018. doi: 0.1161/CIRCULATIONAHA. 188.036418. [Epub ahead of print].

Another LEADER subgroup analysis evaluated the imbalance in gallbladder events in patients randomized to the liraglutide treatment arm (abstract 725). Nauck *et al.* reported that in LEADER, the overall risk of acute gallbladder disease was more common with liraglutide versus placebo (n=141 [3.0%] vs. n=88 [1.9%], respectively; HR 1.60, 95% CI 1.23-2.09). There were comparable increases in all four categories: uncomplicated, complicated gallbladder stones, cholecystitis, and biliary obstruction. Cholecystectomy also occurred more frequently in the active treatment arm, although the proportion of patients requiring subsequent cholecystectomy following a gallbladder event was similar between treatment groups (~58%). There was no difference in baseline demographics or characteristics and gallbladder events appeared to be weight independent. Based on these data, the investigators recommend further research into relevant mechanisms.

Lastly, given the positive CV outcomes data associated with the GLP-1 RAs, an attractive treatment option in Type 2 diabetes is conversion from insulin to a GLP-1 RA for a given subset of patients. Citarrella and Italian colleagues reported data from a 6-month longitudinal, real-life study in Type 2 diabetes patients following conversion to liraglutide after treatment with basal-bolus insulin therapy and oral agents over a 6-year period (abstract 744). Several outcomes were monitored in two treatment arms: (1) conversion to liraglutide 1.2 mg/day (n=25); and (2) continued insulin therapy including insulin intensification (n=30). At the end of six months, the following parameters favored the liraglutide group when directly compared to insulin intensification: mean HbA1c reduction from 10.6% to 7.6% ($p<0.001$), waist to circumference ratio from 115.0 to 107.6 cm ($p=0.010$), and body weight 95.8 to 86.7 kg ($p=0.023$). Other measurements such as Visceral Adiposity Index, blood pressure, and aminotransferases were statistically significantly improved in the GLP-1 RA arm when compared to baseline. The investigators concluded that conversion from insulin to a GLP-1 RA may be considered in selected patients.

In the new ADA-EASD diabetes treatment guidelines, GLP-1 RAs now have a prominent position as being the favored first injectable ahead of insulin (see page 17). How this new recommendation will affect their popularity remains to be seen. We would also point out that these drugs are the most expensive glucose-lowering agents, with out of pocket costs, depending on dose, of $600-700 per month. Whether this cost is worth the benefits is a decision that needs to be made at an individual level.

Foie Gras

Nonalcoholic fatty liver disease (NAFLD) is a growing burden among the general population as a result of the obesity epidemic, and is particularly heavy in people with Type 2 diabetes. Despite its devastating consequences, NAFLD remains under-recognized and is not generally a top priority in the clinical management of diabetes. In a symposium on NAFLD, several speakers spoke to the necessity of intensifying diagnostic and management practices.

Dr. Christopher Byrne from the University of Southhampton, England discussed NAFLD as an independent risk factor for the development of Type 2 diabetes and CVD. The increased incidence of NAFLD is related to the obesity epidemic, and is present in 25% of the general population. NAFLD is occurring in up to 75% of people with obesity and Type 2 diabetes. Approximately 10-30% of people with steatosis will go on to develop NASH with or without fibrosis. Of those with NASH, 2% will go on to develop cirrhosis. Cirrhosis is associated with a 50% risk of the need for liver transplantation or death. Moreover, both NASH and cirrhosis are significant risk factors for hepatocellular carcinoma.

Clearly with these consequences, intensified screening and treatment efforts are needed. Dr. Laurant Castera from France discussed the pros and cons of different screening techniques for NAFLD. Serum biomarkers are easy to measure, but 80% of people with NAFLD have normal transaminase levels. In an attempt to improve its sensitivity, a fibrosis 4 (FIB4) score may be calculated. The FIB4 score is a composite of age, AST, and platelet count (https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4). Ultrasound detects steatosis and is easily available, but has low sensitivity for NAFLD, especially in people with obesity. A newer, non-invasive imaging technique, known as FibroScan®, measures both steatosis and liver stiffness, an indicator of liver fibrosis and cirrhosis. Czernichow and colleagues reported that the diagnostic performance of FibroScan in patients with Type 2 diabetes showed good accuracy (abstract 1190). FibroScan is not widely used in the US, however.

There was also some disagreement among the presenters as to the importance of MR techniques to diagnose NAFLD. While MR spectroscopy has superiority over both ultrasound and FibroScan, and is generally favored in the US, it may not be practical for clinical use in most countries. Liver biopsy remains the gold-standard for diagnosing NAFLD.

Dr. Hannele Yki-Järvinen from Helsinki, Finland reviewed the evidence for options to treat NAFLD, including specific lifestyle modifications and medications. Since 37% of people with NASH will die of CVD, it is important that therapy choices also target cardiac risk factors. Weight reduction is highly successful in reversing NAFLD. In a dose-dependent relationship, NAFLD reversal occurs in more people with a greater amount of weight loss. Between 75-100% of people will have NAFLD reversal when 7-10% of baseline body weight is lost (Wong J., *Hepatology* 2018 in press). With weight loss, NASH resolves and fibrosis regresses, as documented by liver biopsy. Weight loss achieved through bariatric surgery is shown to cure even late-stage fibrosis, as long as portal hypertension is not yet present. If weight loss cannot be achieved, maintaining a low saturated fat diet has benefits, as does avoidance of alcohol.

Figure 11. Effect of anti-diabetes agents on NAFLD

*Medication**	*Steatosis*	*Fibrosis*	*RCT*
Thiazolidinediones†	↓↓	↓	Yes
GLP-1RAs	↓	↓	Yes
SGLT2 Inhibitors	↓	No data	Yes
Insulin	↓	No data	Yes
DPP-4 inhibitors	↔	No data	Yes
Metformin	↔	No data	Yes
Sulfonylureas	No data	No data	Yes

* No drug therapy is currently approved by the FDA for any stage of NAFLD

† Pioglitazone is recommended for the treatment of NAFLD by multiple guidelines from the American Society of Gastroenterologists, NICE, and the EASD/EASL/EASO.

For medication options, the clear choice is pioglitazone, a TZD, which is shown to have benefit for people with NAFLD, regardless of Type 2 diabetes status. Approximately 50% of people on pioglitazone will have resolution of NASH over a one-year period. While not FDA approved for NAFLD, pioglitazone is recommended in multiple professional guidelines* (Figure 11). Regression of body fat and liver fat is also seen with GLP-1RA use, and therefore can be considered as a therapeutic option. Vitamin E 800 IU/day is also generally recommended. While statins do not have a direct effect on NAFLD, they should be encouraged for CVD risk reduction and now have a proven safety record in people with this form of liver disease. In the next year or so, trial data will be available on additional non-glycemic disease modifying agents such as obeticholic acid, elafibranor, cenicrivinec, and selonsertib.

Clearly, given the high prevalence of NAFLD and its link to CVD, hepatocellular carcinoma, and increased mortality, screening and treatment of NAFLD needs to become a priority for clinicians managing patients with Type 2 diabetes and/or obesity.

Another Neutral DPP-4 Inhibitor CVOT

Results were presented at a large symposium on the *CV and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA)*. This CV outcome trial (OT) involving linagliptin, a DPP-4 inhibitor, was designed to fulfill regulatory requirements for CV safety for new glucose lowering agents in Type 2 diabetes, and follows similar trials with other members of this class. In contrast to SAVOR-TIMI 53, EXAMINE, and TECOS, CARMELINA chose to also examine renal outcomes and enrolled more patients with existing renal impairment. This renal focus was enabled since linagliptin is primarily excreted via bile and the gut, as opposed to renal excretion, and is therefore thought of as a DPP-4 inhibitor that is easier to use in CKD patients—i.e. no dose adjustments required with declining eGFR.

CARMELINA was a double-blind, placebo-controlled trial in people with Type 2 diabetes at high risk of CV and/or renal events. The primary endpoint was time to first occurrence of CV death, non-fatal MI, or non-fatal stroke (referred to as major adverse CV events [MACE]). In 27 countries, 6980 patients were randomized 1:1 linagliptin or placebo, and had a mean age 66±9 years, HbA1c 8.0 ±1.0%, BMI 31±5 kg/m^2, and an average duration of diabetes for 15±9 years. 57% of patients had established CVD, 74% had baseline kidney disease, and 33% had both CV and kidney disease.

Participants treated with linagliptin had an overall lower HbA1c throughout the trial (-0.36% [95% CI -0.42, -0.29], p<0.0001). For the primary MACE outcome, no differences were detected between the linagliptin and placebo groups (HR 1.02 [0.059, 1.17]). Also, all-cause mortality was high but similar in both groups: linagliptin n=367, placebo n=373 (HR 0.98 [0.84, 1.13]). This is not at all surprising and entirely consistent with prior DPP-4 inhibitor CVOTs. In contrast to saxagliptin in SAVOR-TIMI 53, however, no signal was seen for increased risk heart failure hospitalization (HR 0.90 [0.74,1.01]). The only significant positive finding of the study was the time to first progression of albuminuria, which occurred in fewer people receiving linagliptin than placebo (HR 0.86 [0.78, 0.95], p<0.003). Also, the benefit in reducing microalbuminuria progression was also reflected in the secondary, microvascular composite outcome, which favored linagliptin (HR 0.86 [0.78, 0.95], p<0.0032). In summary, CARMELINA demonstrated CV safety but not CV efficacy for linagliptin in high-risk patients with Type 2 diabetes and could potentially signal a long-term protective benefit on diabetic kidney disease.*

So Many Posters, So Little Time....

What is Hypoglycemia?

Dr. Simon Heller, from the University of Sheffield, UK, presented an important update on hypoglycemia thresholds and terminology. Hypoglycemia has been defined as ≤70 mg/dl, ever since a working group was formed in 2004 by the ADA in order to advise the FDA how hypoglycemia should be used as an endpoint in diabetes intervention studies. In addition, severe hypoglycemia was defined as symptoms requiring assistance from another person for treatment, independent of the glucose level. The 70 mg/dl threshold was criticized because there was little evidence that it was clinically significant and also that plasma glucose may fall to even lower levels in many non-diabetic healthy people.

As a result of ongoing debate about the threshold designation, the International

Hypoglycemia Study Group (IHSG) was formed in 2013 to bring together a group of clinicians and investigators with expertise in hypoglycemia. This group examined existing evidence for what should constitute hypoglycemia, and Dr. Heller cited many key concepts in thinking about hypoglycemia thresholds. For instance, symptoms occur at different glucose levels. People with impaired awareness may not have symptoms, and asymptomatic hypoglycemia is increasingly being found as a result of continuous glucose monitoring (CGM) in clinical trials. The value of having a standardized hypoglycemia definition is to enable comparisons of safety and efficacy between different therapies and interventions. In the IHSG's evaluation, it became clear that with 70 mg/dl, while still relevant as an alert level to signal the need for potentially altering therapy, there was little evidence that this impacted quality of life or caused any adverse health consequences. In contrast, severe hypoglycemia requiring outside intervention has high clinical relevance, but is an infrequent event in most trials and may be underpowered to detect differences between interventions. Thus, the IHSG made recommendations for the addition of an intermediate level, which is associated with impaired cognition and increased frequency of arrhythmias, as well as predictive of mortality, impaired awareness, and risk of severe hypoglycemia. Many clinical studies showed that glucose between 50-55 mg/dl meets this criteria, and the IHSG focused on the threshold of <54 mg/dl (or 3 mmol/l). The new IHSG recommendation for a three-tier definition of hypoglycemia was accepted by the ADA and EASD, and outlined in two simultaneous articles in *Diabetes Care* (2017; 40: 155-157) and *Diabetologia* (2017; 60: 377).

Mortality and Other Major Adverse Outcomes Among Patients with Type 2 Diabetes

J. vor dem Esche from Germany presented the results of a meta-analysis he conducted to quantify fatal and non-fatal, but potentially life-threatening, events among patients with Type 2 diabetes (abstract 92). Data were derived from 72 randomized, controlled clinical trials. Annual mortality rate was 2.4% (30,221 fatal events during 1,342,482 patient-years), with approximately 44% of the mortality events being non-CV death events. The annual rates of serious infections, cancer, heart failure, non-fatal myocardial infarction, and non-fatal stroke were 1.5%, 1.2%, 1.2%, 1.1%, and 0.8%, respectively. The presenter concluded that the focus of clinical trials on the CV morbidity and mortality of new antihyperglycemic treatment strategies does fully characterize the complications associated with Type 2 diabetes.

Figure 12. Age-Standardized Rates of Infection-Related Hospitalizations in the US by Diabetes Status, 2000 – 2014

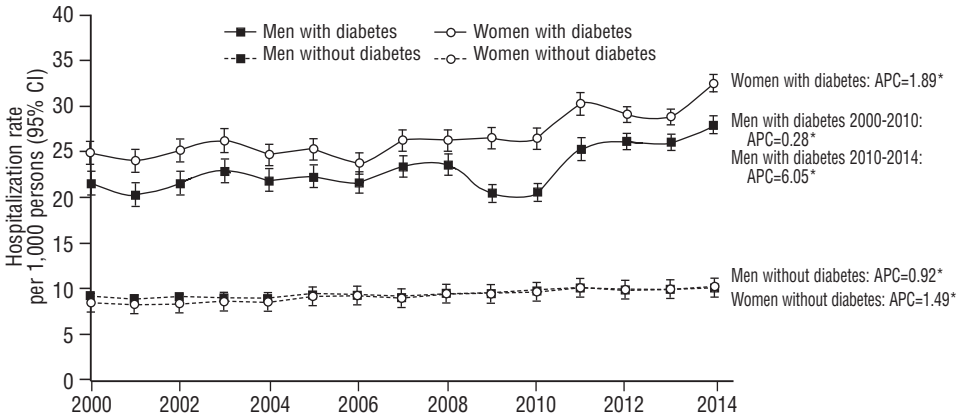


Figure age-standardized rates of infection-related hospitalizations, per 1,000 persons, in men and women with and without diabetes between 2000 and 2014.

APC=annual percent change, *indicates that the APC is significantly different from zero at alpha=0.05.

Metformin and B_{12}

Yang and Chinese associates conducted a meta-analysis of 30 controlled trials to compare the risks of vitamin B_{12} deficiency, anemia, and neuropathy in diabetes patients treated with metformin versus those whose treatment did not include that medication (abstract 706). A random-effect model was first used for the analyses, and a fixed effect model was used for those analyses with a low-to-moderate heterogeneity (I^2<50%).

Metformin use was associated with a significantly increased risk of vitamin B_{12} deficiency (RR=2.28; 95% CI [1.63, 3.21]; p<0.001; I^2=62%), significantly lower B_{12} concentration (mean difference, -64.71 pmol/l [-75.52, -53.91 pmol/l]; p<0.001; I^2=87%), and significantly greater decrease in serum vitamin B_{12} concentration from baseline (mean, -14.7% [-18.0, -11.4%]; p<0.001; I^2=33%). Evaluated in only a few studies, there was no significant difference in risks of anemia (4 studies, 4070 patients: RR=0.93 [0.79, 1.09]; p=0.36; I2=0%) or neuropathy (6 studies, 1058 patients: RR=0.84 [0.62, 1.13]; p=0.25; I^2=60%) between patients using versus not using metformin.

Based on their study results and the fact that vitamin B_{12} deficiency can lead to serious clinical consequences, the investigators recommended vitamin B_{12} supplementation to prevent/treat vitamin B_{12} deficiency in patients with diabetes being treated with metformin therapy. In addition, they noted the need for high-quality studies assessing the association of metformin use with anemia and neuropathy in patients with diabetes.

Rate of Infection-related Hospitalizations Increasing in Patients with Diabetes

Harding and American co-workers estimated infection-related hospitalizations during 2000-2014 in adults aged ≥18 years with and without diabetes in the general US population (abstract 1109). Infection-related hospitalization rates were calculated using the National Inpatient Sample for the number of discharges (ICD-9 CM primary diagnosis code: 001-139, 480-486, 041.12, 682, 785.4, 040.0, 590.0; 060-066; 080-088; 042, 997.31, 136.9; 998.5) and the National Health Interview Survey for population estimates by diabetes status. Joinpoint regression was used to assess trends over time.

Overall, rates of infection-related hospitalizations in the US increased over the period of 2000 to 2014. Adults with diabetes had a significantly greater excess risk of infection-related hospitalizations than those without diabetes, and this excess risk increased significantly over time (Figure 12).

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

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Diabetes 2018 Test

***V**olume 38*

The post-test and evaluation must be completed on-line (not by US mail or fax) at https://yale.cloud-cme.com/aph.aspx?EID=8735&P=3000&CaseID=393, within the Content and Tests folder.

1. Age at onset of Type 1 diabetes was shown to be a strong predictor of cardiovascular (CV) outcomes and survival.
   a. True
   b. False

2. Which of the following was not revealed by the UKPDS study?
   a. Co-morbidities pre-date the diagnosis of Type 2 diabetes in half of patients.
   b. Metformin confers CV benefit in Type 2 diabetes, supporting it as initial therapy in treatment guidelines.
   c. Hyperglycemia combined with hypertension, but not alone, is a risk factor for coronary heart disease.
   d. More effective glucose control can be achieved with earlier introduction of combination therapy.

3. Advances in insulin research, resulting in the availability of newer agents that more closely mimic the pharmacodynamics of endogenous insulin, have surprisingly not affected the cost-of-treatment compared with older agents.
   a. True
   b. False

4. In randomized-controlled trials, physician-led titration of glargine-300 significantly improved glycemic control versus patient self-titration without increased hypoglycemia risk.
   a. True
   b. False

5. Investigational, ultra rapid-acting bolus insulins (e.g., lispro, aspart) were shown to have which of the following potential benefits, as compared to their progenitors?
   a. faster onset of effect
   b. improve postprandial glucose control.
   c. reduced hypoglycemia
   d. all of the above

6. Which of the following medications improves HbA1c, body weight, and blood pressure in Type 2 diabetes?
   a. DPP-4 inhibitors
   b. GLP-1 receptor agonists
   c. SGLT2 inhibitors
   d. both (b) and (c)

7. Data presented at the EASD meeting suggest that patients with Type 1 diabetes should avoid exercise to minimize hypoglycemia risk.
   a. True
   b. False

8. In a population-based cohort study, older (≥66 years) hospitalized patients with diabetes who began insulin after discharge had a similar risk for death or readmission during the 30 days after discharge, as compared to those who received oral glucose-lowering medications.
   a. True
   b. False

9. Which of the following statements is true based on evidence from the EMPA-REG OUTCOME trial?
   a. Empagliflozin decreases the risk of CV mortality and hospitalization for heart failure, regardless of baseline CV risk (based on TIMI Risk Score for Secondary Prevention).
   b. Empagliflozin confers CV protection, regardless of level of kidney function, despite the diminished impact on HbA1c at reduced eGFR.
   c. Empagliflozin slows decline in renal function in patients with existing cardiovascular disease (CVD) and nephrotic-range proteinuria (urine albumin:creatinine ratio [UACR] ≥2200 mg/g).
   d. All of the above.

10. Early evidence suggests that glucagon administered intranasally does not confer the same benefit as intramuscular administration to correct severe hypoglycemia.
   a. True
   b. False

11. One difference between hybrid closed-loop (HCL) insulin pumps and traditional pumps is that the basal insulin rate with HCL, when in auto-mode, adjusts itself per algorithms based on fluctuations in sensor glucose values.
   a. True
   b. False

12. According to results of the phase 3 EASE studies, which of the following effects was not observed when empagliflozin 2.5 mg was added to insulin in Type 1 diabetes patients?
   a. increased DKA risk
   b. reduced HbA1c
   c. modest weight loss
   d. decreased insulin requirements

13. Evidence from randomized, controlled CV outcomes studies have shown reductions in CV events in high-risk patients with Type 2 diabetes with all of the following GLP-1 RAs, except.
   a. liraglutide
   b. semaglutide
   c. lixisenatide
   d. albiglutide

14. In the 2018 ADA-EASD treatment guidelines for Type 2 diabetes, metformin is no longer considered the best initial choice of glucose-lowering therapy.
   a. True
   b. False

15. According to the 2018 ADA-EASD guidelines, which of the following is the first consideration to determine the best next medication if additional glucose-lowering is needed after lifestyle changes and metformin?
   a. the risk of hypoglycemia
   b. the presence of fatty liver disease
   c. the presence of CVD
   d. the presence of microvascular pathology

16. In an uncontrolled study, testosterone treatment of hypogonadism in men with diabetes was shown to improve their metabolic control.
   a. True
   b. False

17. Nonalcoholic fatty liver disease an independent risk factor for the development of Type 2 diabetes and CVD.
   a. True
   b. False

18. FIB-4, a simple calculation based on age, AST, and platelet count, is an inexpensive method that may assist in identifying Type 2 diabetes patients at risk of adverse liver outcomes.
   a. True
   b. False

19. More than 80% of deaths in patients with Type 2 diabetes are due to CV events.
   a. True
   b. False

20. The risk of infection-related hospitalization is decreasing among patients with diabetes in the United States, perhaps related to advances in the appropriate use of antimicrobial agents.
   a. True
   b. False

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