Diabetes 2018

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Diabetes 2018

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Diabetes**2018**

From the 78th Annual Scientific Sessions of the American Diabetes Association

***J**uly 2018*

Dear Colleague:

Time restraints prevented many of you from attending the 78th Annual Scientific Sessions of the American Diabetes Association (ADA) which was held last week in Orlando, FL. 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: July 2018 to December 31, 2018.

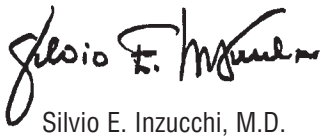
After successfully completing the program, you will be able to:

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

Given the recent explosion of information on diabetes, as well as its relationship to cardiovascular diseases, we began publishing this newsletter series 19 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

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



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Professor of Medicine
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Educational Needs

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

Learning Objectives

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

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

Target Audience

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

Educational Methods

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://goo.gl/XWW7KT. 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*™.

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Diabetes**2018**

Editors' Summary

In this issue of the ***Diabetes 2018*** monograph, we summarize important new diabetes information that was presented at the *78th Annual Scientific Sessions of the American Diabetes Association (ADA)* in Orlando, FL.

The ADA and EASD are in the process of revising their joint guidelines for the management of hyperglycemia in Type 2 diabetes. The committee's major consensus opinions are:

- 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 cardiovascular disease (CVD), other co-morbidities, and risk for specific adverse effects, particularly weight gain and hypoglycemia, safety, tolerability, and cost. Substantial new data have been published since the last iteration of these guidelines in 2015, showing clear advantages of specific drugs in the SGLT2 inhibitor and GLP-1 RA drug classes based on cardiovascular (CV) outcomes.
- When injectable therapy is needed for glucose-lowering, GLP-1 receptor agonists (RA) should be considered as the first choice over insulin.
- 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 inhibitor, or prandial insulin.
- Access, treatment cost, and insurance coverage should all be considered when selecting therapeutic strategies.

With regard to key knowledge gaps and questions, the main issues raised pertained to the role of anti-obesity therapies; ways to preserve beta cell function; the still questionable role of metformin as initial therapy; whether the CV benefits of SGLT2 inhibitors and GLP-1 RAs will extend to lower risk patients; whether these drugs have added CV benefits when used in combination; the need for better insulin sensitizers and for better and safer insulins; and, the lack of data on how to best manage Type 2 diabetes patients with fatty liver disease, the frail elderly, and adolescents.

We believe the writing committee has done an extraordinary job in synthesizing recent data and incorporating them into an outstanding consensus document. The public is invited to review the draft at https://professional.diabetes.org/2018EASDconsensus. Comments can be submitted to adacomments@diabetes.org until 11:59 PM EDT on Monday July 2, 2018.

New data from the EMPA-REG OUTCOME and CANVAS trials were presented at the *2018 ADA Scientific Sessions*, refining our understanding of the CV and renal benefits of SGLT2 inhibitors for our patients with Type 2 diabetes.

By way of background, the EMPA-REG OUTCOME trial (7,020 Type 2 diabetes patients with Type 2 diabetes with overt CV complications), empagliflozin reduced the risk of the primary outcome of 3-point major adverse CV events (MACE), comprised of CV death, non-fatal MI, and non-fatal stroke, by 14% ($p=0.04$) versus placebo on top of standard of care. This was driven by 38% and 35% relative risk reductions in CV mortality and all-cause mortality,* respectively (both $p<0.0001$). Empagliflozin also reduced heart failure hospitalization by 35%* ($p=0.002$) and progression of chronic kidney disease (CKD) by 39%* ($p<0.001$). Further analyses of these data showed that the SGLT2 inhibitor slows renal function decline in patients at high risk for progression of their kidney disease.* At this year's *ADA Scientific Sessions*, EMPA-REG OUTCOME trialists reported that adjustments for control of CVD risk factors (blood pressure, LDL-cholesterol, HbA1c) did not affect the hazard ratio (HR) for study drug vs. placebo on renal outcomes* (abstract 524-P).

In the CANVAS trial of 10,142 Type 2 diabetes patients, the primary MACE endpoint was reduced 14% in the canagliflozin arm as compared to placebo ($p<0.0001$ for noninferiority; $p=0.02$ for superiority). None of the individual components of MACE, however, met the test for statistical significance. In contrast, hospitalization for heart failure was reduced by 33% (HR 0.67 [0.52-0.87]). Both progression of albuminuria (HR 0.73 [0.67-0.79]) and the prespecified composite "hard" renal outcome (sustained reduction in eGFR, the need for renal replacement therapy, or renal death; HR 0.60 [0.47-0.77]) favored the canagliflozin-treated patients.

At this year's *ADA Scientific Sessions*, CANVAS investigators reported on CV outcomes in the 2,039 individuals with CKD (eGFR <60) (abstract 258-OR). Notably, and as seen with other SGLT2 inhibitors, reductions in HbA1c and body weight with canagliflozin were less in these patients than in those without CKD (-0.43 vs. -0.64%, p for heterogeneity <0.0001, and -1.16 vs. -1.43 kg, $p=0.0002$). Yet, the relative effects on the primary and most other CV outcomes were similar across four eGFR subgroups (≥90, 60 - <90, 45 -<60, <45). The investigators concluded that, despite smaller glycemic effects in patients with reduced eGFR, the cardioprotective benefits of canagliflozin were maintained,* dovetailing with the empagliflozin findings.

In the monitoring space, attendees of the symposium "Understanding the Hybrid Closed-Loop (HCL) Pump" learned more about MiniMed® 670G, a HCL comprised of a continuous glucose monitoring (CGM) sensor/transmitter, an insulin pump (that also displays real-time glucose data), and a glucose meter. Results of a larger study of "real world" HCL use (by 13,906 patients since the system's US approval) (abstract 960-P) confirmed the benefits observed in the pivotal study upon which the approval was based. Investigators compared glucose metrics between 258,415 patient-days in the initial open-loop manual mode and 724,220 patient-days after starting the closed-loop auto mode. For all patients (≥7 years of age*) time-in-range (70-180 mg/dL) increased from 63.2% to 71.4%, time <70 and <50 mg/dL decreased from 2.6% to 2.1% and from 0.4% to 0.3%, respectively, and time >180 mg/dL decreased from 34.2% to 26.6%. Study results of other "next-gen" CGM ways to monitor glucose were also presented, including the Eversense (abstract 901-P) and FreeStyle Libre Flash CGM System (abstract 72-LB).

Of interest to us was a symposium focused on monogenic diabetes (caused by a mutation or deletion in a singe gene), which affects up to 5% of all people with diabetes, as well as diabetes as an immune-related adverse event of immune checkpoint inhibitors (ICI) (e.g., anti-PD-1, anti-PD-L1, and anti-CTLA-4) being used to treat solid tumor malignancies (abstract 204-LB).Also interesting was a presentation by Dr. Toni Moran from the University of Minnesota during which cystic fibrosis-associated diabetes was discussed: By age 40, >50% of CF patients have diabetes and even more (~80%) in those with the most severe CF transmembrane conductance regulator genotypes.

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.*

Diabetes2018

From the 78th Annual Scientific Sessions of the American Diabetes Association ■ Orlando, FL

2015 2016 2017 **2018** 2019 2020 2021

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

Volume **37** ■ June 24, 2018 ■ Issue **1**

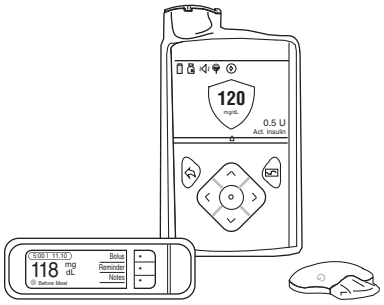
The Hybrid Closed-Loop Insulin Pump: The Latest Advancement in T1DM Management

Despite much progress in the treatment of Type 1 diabetes, most patients do not achieve the desired quality of glycemic control and remain at risk for severe hypoglycemia, diabetic ketoacidosis, and long-term complications. Some insulin pump systems discontinue insulin delivery in response to existing or predicted low sensor glucose values, whereas hybrid closed-loop (HCL) systems provide automatic basal rate adjustments with the patient still in charge of meal time boluses. (Fully closed-loop systems may one day handle both basal and boluses automatically.)

In the symposium "Understanding Hybrid Closed-Loop Pump", conducted on the first day of the 78th ADA Scientific Sessions in Orlando, Elizabeth Doyle, nurse practitioner from the Yale Diabetes Center and the Yale School of Nursing, New Haven, CT, discussed "What Clinicians Need to Know". First, she reviewed the components of MiniMed® 670G, currently the only available HCL pump. The system includes a continuous glucose monitoring (CGM) sensor/transmitter, an insulin pump (that also displays real-time glucose data), and a glucose meter (Figure 1).

In contradistinction to basal rates that are programmed into an insulin pump for standard pump therapy, the basal rate with HCL (when in "auto mode") adjusts itself every five minutes, according to an algorithm based on fluctuations in sensor glucose values (i.e., current and recent past values and anticipated future level), targeting 120 mg/dL. However, HCL is not designed to adjust for rapid changes in glucose levels (e.g., missed meal dose), therefore high glucose values must continue to be corrected, if needed, with the bolus feature. Similarly, and as mentioned, the patient remains fully in charge of meal-time insulin delivery, since HCL, even with currently available rapid-acting insulins, cannot possibly 'catch-up' with typical post-prandial glycemic excursions. HCL will also terminate auto mode, switching back to manual mode, if the sensor fails or if the patient's glycemia is not responding predictably to auto mode basal rate changes.

Figure 1. Hybrid Closed-Loop Insulin Pump: MiniMed® 670G



Next, Doyle reviewed results of a multi-center study of Type 1 diabetes patients (HbA1c <10%), which formed the basis for FDA's approval of the MiniMed® 670G. Eligible patients—30 adolescents (age, 14-21) and 94 adults (age, 22-75)—had been treated with an insulin pump, with or without CGM, for at least 6 months (Bergenstal *et al*., *JAMA* 2016; Garg *et al*., *Diabetes Technol Ther*. 2017). Initially, study patients wore the pump and CGM as a standard pump during a 2-week run-in period, after which they were transitioned to auto mode for the next 3 months.

HbA1c decreased from 7.4% at baseline to 6.9% at study end, with a substantial increase (from 38% to 62%) in the proportion of patients meeting goal HbA1c of <7.0%. HCL simultaneously reduced values <50 and <70 mg/dL and increased the amount of time spent in the target range to >70% for the day/night period (each p<0.001, Table 1). The amount of time in hyperglycemia was decreased. There were no episodes of diabetic ketoacidosis (DKA) and no severe hypoglycemic events in over 12,000 patient-days of HCL use, a vast improvement over intensive insulin therapy as reported in the DCCT trial (62.0 severe hypoglycemia

events per 100 patient-years) (DCCT Research Group, *N Engl J Med*, 1993) and sensor-augmented pump treatment (20 events per 100 patient-years) (Tamborlane *et al*., *N Engl J Med* 2008).

Complementary to, and consistent with, the pivotal study results were findings, from "real world" use of HCL by 13,906 patients since US approval of MiniMed® 670G, presented this week by Agrawal and coworkers from California (abstract 960-P). The investigators compared glucose metrics between 258,415 patient-days in the initial open-loop manual mode and 724,220 patient-days after starting the closed-loop auto mode (abstract 960-P). Time-in-range (70-180 mg/dL) increased from 63.2% to 71.4%, time <70 and <50 mg/dL decreased from 2.6% to 2.1% and from 0.4% to 0.3%, respectively, and time >180 mg/dL decreased from 34.2% to 26.6%.

Doyle also summarized data recently presented at the 2018 Endocrine Society meeting, which showed comparable efficacy and safety in children to that observed in adolescents and adults, with no episodes of DKA or severe hypoglycemia and no serious device-related adverse events. Updated results in children were presented this week (abstract 960-P): In 479 patients between 7 and 13 years of age with Type 1 diabetes,* HCL increased time spent in the target glucose range (from 52.3% to 64.9%).

Table 1. Sensor Glucose Values Among Type 1 Diabetes Patient Using HCL System

	% Time in Range Over 24 Hours	
	Run-in	*Study*
>300 mg/dL	2.3	1.7
>180 mg/dL	27.4	24.5
71-180 mg/dL	66.7	72.2
≤70 mg/dL	5.9	3.3
≤50 mg/dL	1.0	0.6
Within-day SD	2.8	2.6

Doyle ended her presentation answering the question, "Who should you prescribe HCL therapy for?" Approved for Type 1 diabetes patients over age 14, HCL also has been used successfully in some patients at Yale with insulin-dependent Type 2 diabetes,* and study results show efficacy and safety in younger patients with Type 1 diabetes. She noted that potential candidates for HCL must require at least 8 units of insulin daily, proficiently and routinely carb count, and check their blood glucose at least 4 times daily. (They will need to check, on average, 3-4 times daily even while in HCL auto mode.) And, importantly, candidates must be realistic; while representing a true advance in diabetes management, HCL does not control glycemia like a functioning pancreas and technical issues may arise, as with any pump and sensor system. For example, pump sites can fail, insulin catheters can become clogged, and sensor accuracy can fluctuate, etc. As Doyle summarized, patients cannot simply "turn on an HCL pump and forget that they have diabetes".

Clinical trials with HCL involve highly motivated patients and the results may not necessarily reflect those that might occur after more widespread use. Even the 'real-world' data reported by Agrawal involve patients who were on waiting lists to try HCL and these individuals may also have been highly selected.

Metformin: Still First-Line Therapy in T2DM?

A heated debate conducted on the opening day centered around the question, "Should Metformin Remain the First-Line Therapy for Type 2 Diabetes?" Taking the affirmative position was Dr. Vanita Aroda from the Brigham and Women's Hospital, Boston, MA, and defending the position that change is overdue was Dr. Alice Cheng from the University of Toronto, Canada.

Dr. Aroda remarked that there is a substantial evidence base, accumulated over 2 decades, supporting metformin's efficacy, safety, and role as initial therapy. This coupled with its affordability ($4/month) has resulted in its recommendation as first-line therapy (after diet and exercise, barring contraindications) in most current treatment guidelines, including those of the ADA/European Association for the Study of Diabetes and the International Diabetes Federation.

Beyond robust HbA1c reduction (1-1.5%), exceeding that of many other agents, metformin confers cardiovascular (CV) benefit to patients with Type 2 diabetes,* shown first in a prespecified (albeit small) subinvestigation of overweight patients enrolled in the UK Prospective Diabetes Study (UKPDS-34)—39% reduction in risk of MI (p=0.010) (*Lancet* 1998), and more recently in the HOME study of Type 2 diabetes patients on insulin (vs. placebo, p=0.02; Kooy *et al., Arch Intern Med* 2009) and the SPREAD-DIMCAD study of Type 2 diabetes patients with coronary artery disease (vs. sulfonylurea [SU], p=0.026; Hong *et al., Diabetes Care* 2013), with 39% and 46% reduction in expanded major adverse cardiovascular events (MACE), respectively. Subsequently, improved CV outcomes and all-cause mortality* versus sulfonylurea monotherapy were shown in larger observational studies (Johnson *et al., Diabetes Care* 2002; Roumie *et al., Ann Intern Med* 2012; Claesen *et al., J Clin Endocrinol Metab* 2016).

To supplant metformin for first-line monotherapy of Type 2 diabetes, another agent must demonstrate a tangible advantage. To date, such trials that evaluated CV outcomes have been placebo-controlled upon a background of contemporary treatment, primarily metformin (~75% of patients) (Inzucchi, *Diabetes Care* 2017). And, amongst the most prominent studies, EMPA-REG OUTCOME (empagliflozin; Zinman *et al., N Eng J Med* 2015) enrolled only patients with a history of cardiovascular disease (CVD). LEADER (liraglutide, Marso *et al., N Eng J Med* 2016) and SUSTAIN-6 (semaglutide, Marso *et al., N Eng J Med* 2016) included patients older than 50 with overt CVD, and a smaller cohort of patients older than 60 with CV risk factors only. In the latter 2 studies, the point estimate for the primary endpoint was ≥1 for the patients without CVD, suggesting benefit only in those with prevalent macrovascular disease, not the typical patient beginning treatment for Type 2 diabetes. In CANVAS (canagliflozin, Neal *et al., N Engl J Med* 2017), the MACE outcome was also not significantly reduced in the smaller cohort without CVD at baseline (although the heart failure outcome was [Mahaffey *et al. Circulation* 2018]).

Substantial use of metformin in treatment of early disease also stems from the Diabetes Prevention Program (DPP) of overweight patients with impaired glucose tolerance and fasting glucose 95-125 mg/dL who experienced a 31% reduction in new-onset diabetes* over 2.8 years of follow-up relative to placebo (Knowler *et al., N Eng J Med* 2002) and 18% reduction after 10 years (*Lancet Diabetes Endocrinol* 2015).

The safety and tolerability of metformin are well-known, involving GI side effects (nausea, diarrhea) that are mostly self-limited and mitigated

by use of an extended-release formulation, B_{12} deficiency (easily monitored and treated as needed), and the very rare complication of lactic acidosis that most likely occurs in patients with a prevailing contraindication, notable renal failure. This contrasts with the newer agents for which a full understanding of safety profile, especially long-term toxicities, is still being illuminated with broader use in clinical practice.

Dr. Varoda concluded that there is no current evidence for replacing metformin with another agent as foundation treatment for all patients with Type 2 diabetes, in the absence of contraindications, based on its extensive use in clinical practice and demonstrated efficacy, safety, low cost, and possible CV benefits.

Taking the position that change is overdue and that better options are available, Dr. Cheng noted that metformin does not 1) address core defects like other agents do; 2) improve metabolic parameters as other agents do; 3) improve microvascular (renal) endpoints as other agents do; 4) improve macrovascular (heart) endpoints as other agents do in large CV outcome trials; and, 5) improve all-cause mortality as other agents do.

Dr. Cheng noted that several of the newer agents reverse multiple pathophysiological abnormalities (core defects) of Type 2 diabetes involving multiple organs, more so than metformin (Figure 2).

The speaker then affirmed metformin's antihyperglycemic effect, as noted earlier by Aroda, but underscored the importance of improving other metabolic parameters, where metformin does not measure up (i.e., neutral to modest effect on weight and neutral effect on blood pressure and lipids; Table 2).

The next advantage of other agents over metformin, as summarized by Cheng, is their renoprotective effects (versus placebo). Relative risk reduction (RRR) in incident or worsening nephropathy was 39% with empagliflozin* in EMPA-REG OUTCOME (Wanner *et al., N Eng J Med* 2016) and 40% for a similar composite outcome with canagliflozin* in CANVAS. The GLP-1 receptor agonists, liraglutide* in LEADER (Mann *et al., N Engl J Med* 2017) and semaglutide* in SUSTAIN-6, resulted in 22% and 36% RRRs, respectively, in the nephropathy outcome. (However, this was mainly driven by reductions in albuminuria, whereas the SGLT2 inhibitors also appear to slow decline in glomerular filtration rates.)

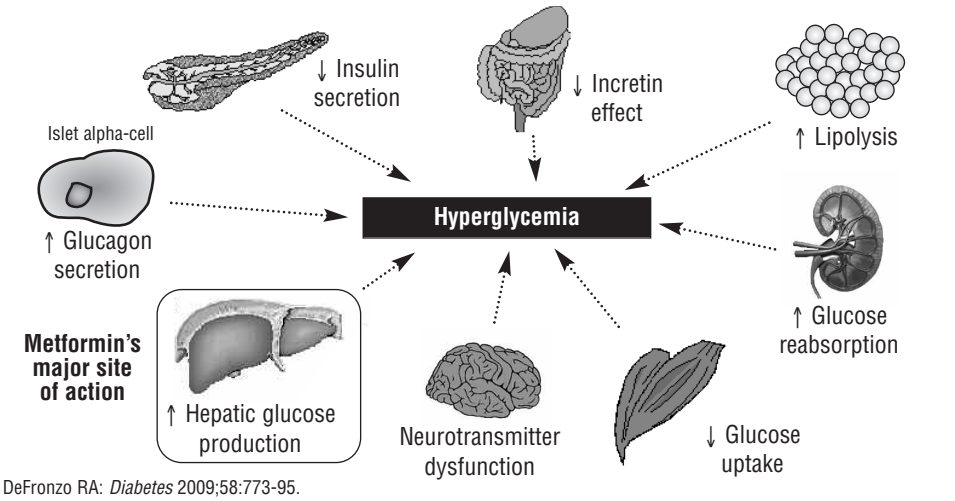
The speaker also noted an advantage of other agents (GLP-1 receptor agonists, SGLT-2 inhibitors) over metformin based on decreases in MACE (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) in large CV outcome studies: EMPA-REG (14% RRR with empagliflozin), CANVAS (14% RRR with canagliflozin*), LEADER (13% RRR with liraglutide), and SUSTAIN-6 (26% RRR with semaglutide*).

The last point of Dr. Cheng's discussion was the improvement in all-cause mortality from other drugs in large CV outcomes trials: a 32% risk reduction with empagliflozin* in EMPA-REG OUTCOME and a 15% risk reduction with liraglutide* in LEADER. No such data exists for metformin. Moreover, positive CV benefits from metformin come from trials with relatively small numbers of patients with a limited number of events (Boussageon *et al., PloS Med* 2012).

Finding a common ground during the Q&A session, the speakers suggested that our focus going foreword should not necessarily be on replacing metformin, but rather on which drug to add and when (perhaps earlier than is typically considered).

We would add that to unseat metformin as foundation therapy in Type 2 diabetes, large head-to-head trials would be required and those are unlikely to ever occur. So, for good or bad (we feel mostly good!), metformin will likely remain the preferred initial drug of choice for many years.

Figure 2. Pathophysiological Abnormalities in Type 2 Diabetes Amenable to Therapeutic Interventions



DeFronzo RA: *Diabetes* 2009;58:773-95.

Table 2. Improvement of Metabolic Parameters

Agent	*HbA1c*	*Weight*	*Blood Pressure*	*Lipids*
Metformin	↓ ↓ ↓	→ ↓	→	→
DPP-4 inhibitors	↓	→	→	→
GLP-1 receptor agonist	↓ ↓ ↓	↓ ↓ ↓	↓	↓ TG, ↑ HDL
SGLT-2 inhibitor	↓ ↓	↓ ↓	↓	↓ TG, ↑ HDL

The New World of Glucose Monitoring

In an afternoon symposium at the 78th Scientific Sessions' opening day, entitled, "Data Data Everywhere…", four presenters addressed several aspects of ambulatory glucose monitoring from interpreting data to optimally engaging the patient. A repeated sentiment from each of the presenters was that while HbA1c monitoring continues to be the gold standard to assess patients with diabetes, meaningful improvements in patient care and outcomes are achieved with careful attention (and intervention, where appropriate) to the evaluation of ambulatory glucose profiles whether obtained via CGM or self-monitoring of blood glucose (SMBG).

Alison Evert, MS, RD, CDE, University of Washington Neighborhood Clinics, Seattle, led the session detailing the evolution of glucose monitoring, starting with urine glucose strips to

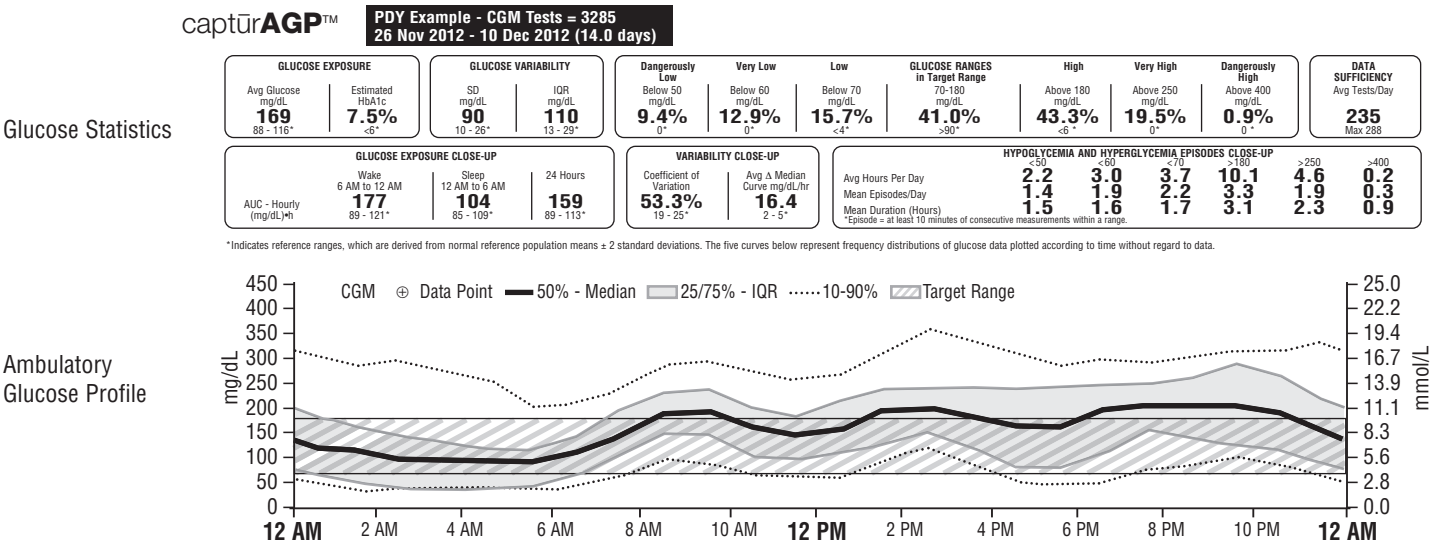
finger stick measures documented by handwritten patient records to present day CGM utilizing sensors and smart phone technology. She recognized the evidence supporting use of HbA1c as the primary indicator for patient assessment, but emphasized the need to utilize other glucose metrics to identify glycemic variation and glucose highs/lows as well as the relationship between these values and food intake, activity, and medication use. Evert advocated that these are the measures to best guide therapeutic decision making. She shared the concept of using mean glucose values and standard deviation (SD) with the goal that the SD should be less than one-half of the mean glucose (ideally, SD less than one-third of the mean glucose, an indicator of relatively low glycemic variation). Essentially, the higher the SD, the higher the glycemic variation. Ultimately, Evert advocated for use of ambulatory glucose monitoring as a new "vital sign" in the monitoring of patients with diabetes.

Use of intermittent CGM to supplement HbA1c testing was further supported by Mary Johnson, RN, BS, CDE, International Diabetes Center, Minnesota, in her presentation: *Ambulatory Glucose Profile (AGP)—The Picture Says It All*. Johnson promoted an international standard that utilizes CGM in a standardized report form referred to as the AGP and now supported by major diabetes organizations. The report displays CGM metrics evaluating 5 ranges of glycemic control: very low (<54 mg/dL), low (<70 mg/dL), target (70-180 mg/dL), high (180-250 mg/dL), and very high (>250 mg/dL). She then demonstrated how these profiles might be used to individualize care and assist in therapeutic decision making. There are 3 components to the profile (Figure 3): (1) a statistical summary; (2) visual display; and (3) daily view. From the patient's perspective, the AGP is simple to visualize and comprehend (versus a spreadsheet or diary) and from the provider's point of view, it creates an efficient way to evaluate data. Johnson shared nine steps to best interpret the AGP: (1) use adequate data (at least 10 days of measures); (2) "mark it up"—meaning edit with meal notations, vacation, snacks, exercise, etc.; (3) ask the patient "what do you see?" and most importantly, LISTEN; (4) identify patterns of hypoglycemia; (5) identify patterns of hyperglycemia; (6) identify areas of wide glycemic variability; (7) compare to past AGPs, reinforcing successful behaviors; (8) agree on an action plan together; and (9) provide the patient a copy and include it in the electronic health record. She concluded that data analysis has markedly improved from the historical paper documentation of SMBG values and dense data provided by CGM to the standardized approach of the AGP, allowing for systematic interpretation and enhanced potential for meaningful patient care decisions.

Patricia Knutsen, NP-C, RN, NMSN, ACNS-BC, CDE, Washington University, St. Louis, introduced the concept of professional CGM and how to avoid pitfalls and optimize outcomes. She began by describing *professional* CGM which is when the practice owns the devices and uses them in multiple patients. Patients wear them for a defined period, then return for download/data analysis. They are particularly useful for individuals who are interested in CGM, but unwilling or unable to qualify by their insurer for a patient-owned device. Several companies support professional CGM including, but not limited to, Abbott, Dexcom, and Medtronic. Considerations when choosing to utilize professional CGM are: blinded data or not (Knutsen recommends unblinding the data to maximize behavior modification), ease of use, alarms, accuracy, ease of downloads, and download reports. From an administrative perspective, she recommends that offices begin with a plan and be prepared to adapt that plan. Steps include: (1) identifying the patient and choice of system/device used; (2) address scheduling issues; (3) identify a team responsible for care of the equipment upon return for cleaning, charging, and putting new kits together; (4) a process for downloading of data and interpretation (this does not have to be a face-to-face visit); and (5) billing. Knutsen shared CPT codes for billing which differ based on device application, device training, and/or data interpretation—each of which is a billable service. Lastly, she reiterated the message that HbA1c monitoring is valuable, but in the modern era CGM and AGPs are essential.

Finally, Margaret Pellizzari MS, MBA, RN, CDE, CDTC, Northwell Health, New York, provided individual case presentations and experiences with the currently available CGM devices, focusing on how to address patients in a constructive

Figure 3. Sample of Standardized Ambulatory Glucose Profile (AGP) (Without Daily View)



Bergenstal RM. *Diabetes Technol Ther.* 2013;15:198-211.

manner. She shared anecdotal experiences and how to individualize conversations to "coach" the patient versus lecture or advise them. She also suggested that rotation of CGM sensor sites is often overlooked. While the data on lipohypertrophy and its impact on CGM accuracy are conflicting (DeSalvo DJ, *et al. Diabetes Care* 2015; 38: e166-67), Pellizzari generally recommends staying within the same body area for one week and then rotate.

Overall, each faculty member at the symposium strongly supported the use of CGM devices, using a standardized AGP and actively engaging patients in the interpretation of data and decision making.

Monogenic Diabetes: Integrating Genetics into your Practice

The diagnosis of Type 1 and 2 diabetes is such a routine occurrence that less common forms of diabetes are often overlooked. Busy clinicians already have so much to cover during initial visits. How do we remember to at least consider other pathophysiological causes? *Monogenic Diabetes* is a term used to describe several conditions in which variation in a single gene results in hyperglycemia. It is also termed *Neonatal Diabetes* when occurring in babies and *Maturity Onset Diabetes of the Young (MODY)* in teenagers and young adults. Many times, these conditions are mistaken for either Type 1 or 2 diabetes, with the chosen glucose-lowering strategy sometimes ineffective. The diagnosis may be suspected clinically, but needs to be confirmed through genetic testing. Yet, such testing remains expensive, and may also not be conclusive. The nuances surrounding these issues were discussed in a symposium on the first full day of this year's Scientific Sessions.

Louis Philipson, MD, PhD from the University of Chicago leads one of several patient registries for monogenic diabetes. He emphasized that monogenic diabetes is under-diagnosed since it affects 1-5% of all people with diabetes, or approximately 1 in 50. There are 13 genes for which mutations or deletions are known to cause diabetes, but there are at least 100 genes for which a mutation could conceptually lead to hyperglycemia. The most common genes affected are hepatocyte nuclear factor 1α (HNF1A; 52%), glucokinase (GCK; 32%), and hepatocyte nuclear factor 4α (HNF4A; 10%), with other genes combined comprising about 6% (Table 3). Diabetes due to mutations in HNF1A and HNF4A may be successfully treated with sulfonylureas, generally at low doses. People with a GCK mutation have hyperglycemia, but generally only have an HbA1c 6-7% that does not progress. Since their hyperglycemia is not associated with long-term complications, it is not usually necessary to treat.

Table 3. Genes for which Mutations or Deletions Cause Monogenic Diabetes

MODY Subtype	*Gene Symbol*	*Gene Name*	*Prevalence*	*Gene Function*	*Other*
3	HNF1A	hepatocyte nuclear factor 1α	52%	transcription factor	sulfonylurea sensitive
2	GCK	glucokinase	32%	glycolytic enzyme	no progression, no treatment
1	HNF4A	hepatocyte nuclear factor 4α	10%	transcription factor	macrosomia & neonatal hypoglycemia
4	IPF/PDX1	insulin promoter factor 1/pancreas-duodenum homeobox protein 1	<6%	transcription factor	permanent neonatal diabetes
5	HNF1B	hepatocyte nuclear factor 1β	<6%	transcription factor	renal cysts & diabetes
6	NEUROD1	neurogenic differentiation 1	<6%	transcription factor	permanent neonatal diabetes
7	KLF11	Kruppel-like factor 11	<6%	transcription factor	
8	CEL	carboxyl-ester hydrolyase/Bile salt-stimulated lipase	<6%	lipase	MODY with exocrine dysfunction
9	PAX4	paired box gene 4	<6%	transcription factor	
10	INS	insulin	<6%	insulin	
11	BLK	tyrosine kinase, B-lymphocyte specific	<6%	transcription factor	
12	ABCC8	ATP-binding cassette transporter sub-family C member 8 (ABCC8), encoding sulfonylurea receptor 1	<6%	subunit within potassium channel in pancreas	
13	KCNJ11	potassium voltage-gated channel subfamily J member 11p	<6%	potassium channel in pancreas	

Miriam Udler, MD, PhD from the Massachusetts General Hospital discussed practical details concerning who to test and how. Classical features of monogenic diabetes include onset in someone <35 years old, with a parental history of diabetes, who is lean or normal weight, and has negative islet cell antibodies. However, while it is important to note that these features are "red flags" that should prompt investigation, they are not overly sensitive. For instance, the presence of

obesity does not exclude monogenic diabetes. In 2012, Shield *et al.* reported the age, BMI, and HbA1c distribution of different forms of diabetes, and developed a MODY calculator (*Diabetologia*. 2012;55:1265-72. doi: 10.1007/s 00125-011-2418-8). This now online tool (www.diabetesgenes.org/content/mody) generates a probability score, which may help support the pursuit of genetic testing. However, Dr. Udler feels that clinical suspicion should be used regardless of score because the calculator was developed using a white, European population and does not take into account C-peptide or autoantibody results, or a history of diabetes in non-parental family members.

Several commercial companies offer testing, usually as either a single gene or a panel of the 5 most common ones. A full list of these genes and their available tests are available through the NCBI Genetic Testing Registry, http://ncbi.nlm.nih.gov/gtr or Concert Genetics, https://www.concertgenetics.com/. There are two different methods for testing: next generation sequencing and deletion/duplication testing. Dr. Udler recommends requesting both methods since diabetes may occur from a deletion of one gene copy, not just mutations. So, false negatives may result from completing just one form of testing. For neonates, free genetic testing is available through the University of Chicago or the University of Exeter, England. For adolescents or adults, testing is generally covered by insurance, although a physician's letter of support is helpful.

Liana Bilings, MD, MMSc from the University of Chicago gave details on how she manages genetic testing for her patients. Two visits are scheduled, separate from routine care, to discuss the benefits, risks, and limitations of genetic testing, complete paperwork, and then later returning to discuss the final results. The main risks and limitations include indeterminate results, testing of genes based on current knowledge and technology, and the difficulty in keeping results fully confidential. The Genetic Information Nondiscrimination Act, passed in 2008, states that no one can be discriminated against by their employers or current healthcare insurance company for having a genetic basis for disease. However, it does not provide protection with regard to disability insurance or future healthcare insurance coverage.

In summary, monogenic diabetes is important to diagnose because management may be altered, especially if it is due to variation in the three most common genes. However, the known genes with variations causing diabetes were discovered in Caucasian populations, so research in additional populations is necessary to make the genetic testing more relevant to everyone. Genetic testing remains very expensive, but this cost is becoming cheaper over time.

So Many Posters, So Little Time....

Peripheral Neuropathy in Prediabetes

Perumbalath *et al.*, from the UK conducted a meta-analysis of 23 studies, all observational, identified by a comprehensive literature search through October 2017 to determine the prevalence of peripheral neuropathy in patients with prediabetes (abstract 552-P). They determined an 18% (95% CI: 13-22%) pooled prevalence estimate, with a high level of heterogeneity between studies (I^2=97%), partly explained by the method of neuropathy assessment. Prevalence depending on the type of test used was: quantitative tests: 16% (3-30%, I^2=95%), physical examination: 24% (7-40%, I^2=83%), questionnaires: 8% (2 -13%, I^2=57%), and combination(s) of the three: 18% (13-24%, I^2=97%). Large, population-based studies using precise and standardized means of identifying neuropathy are required to determine disease burden of peripheral neuropathy in prediabetes. Based on these data, the investigator concluded that routine screening for peripheral neuropathy be strongly considered, with early preventative measures and treatment of painful symptoms. What is not known, however, is whether lowering glucose levels in these patients will help, as has been demonstrated in the past in patients with peripheral neuropathy and frank diabetes.

Liver Fibrosis in Patients with Type 2 Diabetes

Non-alcoholic steatohepatitis (NASH) is very common in patients with Type 2 diabetes, and may progress to fibrosis or even cirrhosis.

Using a clinical database from a national laboratory, Filozof and associates from Spain, US, and UK evaluated progression of liver fibrosis using the 'FIB-4' score over a 4-year period in 334,076 patients (48% male) with Type 2 diabetes (abstract 1570-P). A patient's FIB-4 score is calculated as follows: age (in years) x AST (U/L)/[platelet count (10^9/L) x ALT (U/L)]$^{1/2}$. (See http://gihep.com/calculators/hepatology/fibrosis-4-score/)

The majority of patients had FIB-4 score of Grade 1 (207,629, 75.2%) at baseline (Table 4), suggesting absence of advanced liver fibrosis. Those with low FIB-4 were younger and had lower ALT/AST and higher platelet counts. Mean plasma triglycerides and HbA1C were similar across the fibrosis grade groups.

Among Grade 1 patients, 83% stayed Grade 1, 17% progressed to Grade 2 and 0.7% to Grade 3 or 4 after 4 years. A total of 10% and 27% of patients initially at Grade 2 and Grade 3, respectively, progressed to higher FIB-4 scores, associated with higher risk of adverse liver outcomes. Interestingly, 23%, 7%, and 6% with Grade 2, Grade 3, and Grade 4 regressed. Importantly almost half of the patients at risk of liver outcomes (Grade 3 or 4) had ALT/AST within the normal reference ranges.

Table 4. FIB-4 Score at Baseline and Follow-up

	Baseline (2012)			
Follow-up (2016)	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Grade 1	207,629	17,324	290	234
Grade 2	41,761	50,004	2,002	958
Grade 3	1,015	4,529	950	614
Grade 4	697	2,802	1,203	2,064

Grade 1: FIB-4 < 1.45; Grade 2: FIB-4 1.45 - <2.67; Grade 3: FIB-4 2.67 - <3.25; Grade 4: FIB-4 ≥ 3.25.

The investigators concluded that FIB-4, which is calculated based on mostly routine laboratory parameters, is a simple, inexpensive method that may help identify patients at risk of adverse liver outcomes. Strategies to slow the growth of liver complications and therapeutic options are necessary to mitigate NASH disease burden.

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

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Diabetes2018

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SGLT2 Inhibitors: Risks and Benefits

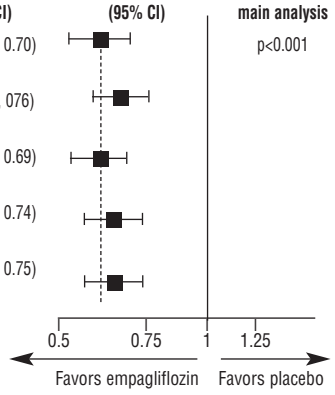
The newest glucose-lowering drug class, the SGLT2 inhibitors, have revolutionized the treatment of Type 2 diabetes, after recognition of their potent beneficial CV and renal effects. In 2015, as reported in this newsletter, the SGLT2 inhibitor empagliflozin in the EMPA-REG OUTCOME trial was found to decrease the relative risk of CV mortality* by 38% and the risk of heart failure hospitalization* by 35% (Zinman *et al., N Engl J Med* 2016). Subsequently, the renal outcomes from this study were reported: a 39% reduction in the progression of chronic kidney disease* (CKD; Wanner *et al., N Engl J Med* 2016). A subsequent CV outcome trial, CANVAS, involving another member of this class, canagliflozin, confirmed benefits in heart failure* and for the kidney,* but not on CV mortality. In addition, however, the new risks of lower extremity amputations and bone fractures were revealed with this specific SGLT2 inhibitor.

In response to these data, the cardiology and nephrology communities have become interested in the class and a series of clinical trials have been initiated to further investigate the potential indications for SGLT2 inhibition in heart failure and CKD, in individuals both with and without Type 2 diabetes.* At this week's ADA Scientific Sessions, many abstracts were presented further investigating their non-glycemic effects.

From the EMPA-REG OUTCOME trial, Wanner and colleagues explored the association between traditional CV risk factors and the benefits of empagliflozin on renal outcomes (abstract 524-P). In the trial, patients were randomized 1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Risk of incident or worsening nephropathy was assessed in the pooled empagliflozin versus placebo groups, after adjustment for the control of BP, LDL-C, and HbA1c, both at baseline as well as during the trial, as time-dependent covariates. "Control" was defined as systolic BP <140 mmHg and diastolic BP <90 mmHg, LDL-C <100 mg/dL, and HbA1c <7.5%. They found no heterogeneity in the effect of empagliflozin on the reduction in the risk of incident or worsening nephropathy between the unadjusted and adjusted analyses, suggesting that improved renal outcomes from the drug were independent of these CV risk factors (Figure 4). Similar results were reported from this group last year as pertaining to the effects of empagliflozin on CV mortality and heart failure hospitalization

Figure 4. Time to Incident or Worsening Nephropathy Adjusted for Time-Dependent Covariates

	Empagliflozin n with event/n analyzed (%)	Placebo n with event/n analyzed (%)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	p-value for main analysis
Main analysis	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)		p<0.001
Adjusted for baseline and time- dependent control of BP (SBP <140 mmHg, DBP <90 mmHg)	525/4124 (12.7)	388/2061 (18.8)	0.67 (0.59, 076)		
Adjusted for baseline and time-dependent control of LDL-C (LDL-C <100 mg/dL)	519/4056 (12.8)	382/2039 (18.7)	0.61 (0.53, 0.69)		
Adjusted for baseline and time-dependent control of HbA1c (HbA1c <7.5%)	525/4123 (12.7)	388/2061 (18.8)	0.65 (0.57, 0.74)		
Adjusted for baseline and time-dependent control of BP, LDL-C and HbA1c	519/4055 (12.8)	382/2039 (18.7)	0.65 (0.57, 0.75)		



Cox regression analysis for time to first event in patients treated with ≥1 dose of study drug. Main analysis did not adjust for baseline or time-dependent control of BP, LDL-C or, HbA1c. BP=blood pressure; DBP=diastolic blood pressure; HbA1c=glycated hemoglobin; LDL-C=low-density lipoprotein cholesterol; SBP=systolic blood pressure.

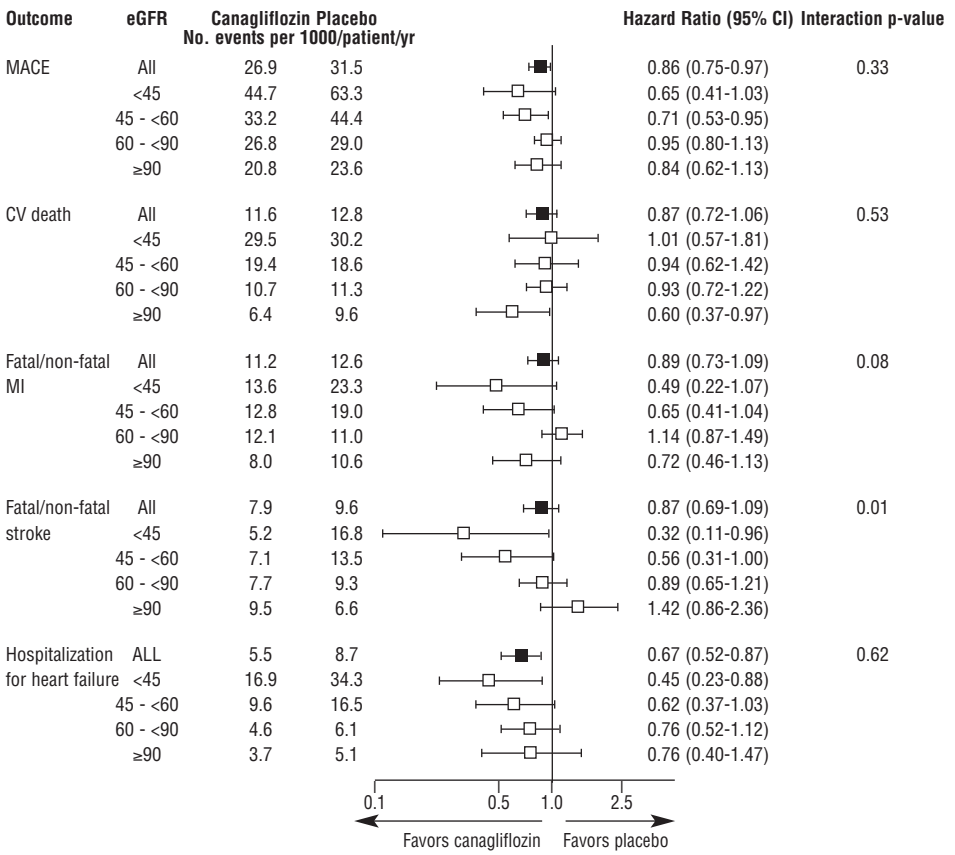
(*Diabetes 2017*, volume 36).

Neuen and colleagues reported on CV outcomes in the CANVAS trial in those individuals with CKD at baseline (abstract 258-OR). The trial included 2039 patients (20.1%) with baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. In this subgroup, the mean age was 68 years, BP 138/76 mmHg, HbA1c 8.3%, eGFR 49, and urinary albumin:creatinine ratio 22 mg/g. Notably, and as seen with other SGLT2 inhibitors, reductions in HbA1c and body weight with canagliflozin were less in these patients than in those with eGFR ≥60 (-0.43 vs. -0.64%, p for heterogeneity <0.0001, and -1.16 vs. -1.43 kg, p=0.0002). However, the effects on BP were similar (-3.89 vs. -4.11 mmHg, p=0.21). Moreover, the relative effects on the primary and most other CV outcomes were similar across four eGFR subgroups (≥90, 60 - <90, 45 - <60, <45), with heterogeneity found only in the exploratory outcome of stroke (Figure 5). The investigators concluded that, despite smaller glycemic effects in those with reduced eGFR, the cardioprotective benefits of canagliflozin were maintained. Similar data have been reported with empagliflozin, indicating a disconnect between the blood pressure and antihyperglycemic effects of this class and its CV benefits (Wanner *et al., Circulation* 2017).

As mentioned, in CANVAS, rates of lower extremity amputations were increased in the canagliflozin arm. The reason behind this new apparent risk is unknown. Ryan and American colleagues investigated the link between canagliflozin and below-the-knee level amputations from a large US claims database involving more than 700,000 patients with Type 2 diabetes initiated on canagliflozin, another SGLT2 inhibitor, or a separate category of glucose-lowering agent (abstract 4-LB). The investigators employed propensity score matching to ensure that the comparisons accounted for differences between the groups. They found no increased risk for amputations in those individuals exposed to canagliflozin as compared to other non-SGLT2 inhibitors (hazard ratio [HR] 0.75, 95% CI 0.40-1.41), or compared to other members of the class (HR 1.14, 95% CI 0.67-1.93). The mean duration of exposure in this study was only 6 months, so any risk beyond this point could not be ascertained. Also, consistent with CANVAS, rates of heart failure hospitalizations were significantly reduced in patients receiving SGLT2 inhibitors.

An investigational drug, sotagliflozin,* is an inhibitor of SGLT2 in the kidney and SGLT1 in the gut. The drug not only induces glucosuria (as all SGLT2 inhibitors do), but also decreases gastrointestinal carbohydrate absorption, blunting

Figure 5. Cardiovascular Outcomes in CANVAS Participants by Baseline eGFR



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

Table 5. Pooled Efficacy and Safety Results from Randomization to Week 52 on a Background of Optimized Insulin Therapy in Tandem1 and 2 Studies

	Placebo (n = 526)	*SOTA 200 mg (n = 524)*	*SOTA 400 mg (n = 525)*
Efficacy: HbA1c Change from Baseline			
LS Mean vs. placebo at week 24, % (p-value)	N/A	-0.36 (p<0.001)	-0.38 (p<0.001)
LS Mean vs. placebo at week 52, % (p-value)	N/A	-0.23 (p<0.001)	-0.32 (p<0.001)
Total Insulin % Change from Baseline at Week 52			
LS Mean (SE), p-value	2.12 (0.959), p=0.028	-4.98 (0.955), p<0.001	-8.21 (0.958), p<0.001
Treatment Comparison vs. Placebo			
LS Mean (SE), p-value	N/A	-7.10 (1.301), p<0.001	-10.33 (1.303), p<0.001
Patients with Safety Event through 52 Weeks			
Any TEAE, n (%)	374 (71.1)	393 (75.0)	390 (74.3)
DKA, n (%)	1 (0.2)	15 (2.9)	20 (3.8)
Severe hypoglycemia, n (%)	39 (7.4)	30 (5.7)	23 (4.4)
Diarrhea, n (%)	27 (5.1)	34 (6.5)	46 (8.8)
Genital mycotic infection, n (%)	15 (2.9)	48 (9.2)	63 (12.0)

postprandial hyperglycemia. As a result, the glycemic efficacy of the drug may be greater than SGLT2 inhibitors. There have been extensive studies to date of sotagliflozin in Type 2 as well as Type 1 diabetes. Pettus and international colleagues reported on two 52-week phase 3 studies (TANDEM 1 and 2) involving adult patients with Type 1 diabetes who were randomized 1:1:1 to placebo, sotagliflozin 200 mg, or sotagliflozin 400 mg after a 6-week period of insulin optimization (abstract 5-LB). In this pooled analyses, outcomes assessed included change in HbA1c, change of daily insulin dose, and safety parameters. Significant HbA1c reductions were observed in the two active therapy groups vs. placebo by 24 weeks, and these were sustained to 52 weeks (Table 5). There were also decreases in insulin requirements mainly due to lower doses at mealtime with sotagliflozin. Finally, less severe hypoglycemia was observed in the sotagliflozin groups, but they did experience more genital mycotic infections, DKA, and diarrhea than the placebo group. The first two adverse events have been reported with SGLT2 inhibitors. The collaborators concluded that sotagliflozin improved glycemic control while reducing insulin needs and hypoglycemia risk, suggesting this to be a potential useful adjunct in the management of Type 1 diabetes. The DKA risk of course remains a concern. Notably, DKA may be 'euglycemic' when it emerges as a complication of use of these agents. This is due to ongoing urinary glucose losses. So good clinician and patient education will be needed if these drugs are ever approved for use in Type 1 diabetes.

Table 6. Cardiovascular and Renal Outcomes with SGLT2 Inhibitors in EXSCEL

Time-to-First Adjudicated Event	*Propensity-matched cohort*	*n*	*Events*	*Adjusted Hazard Ratio (95% CI)*
MACE*	No SGLT2i	709	44	
	SGLT2i	709	28	0.79 (0.49–1.28)
	No DAPA	354	22	
	DAPA	354	11	0.55 (0.26–1.15)
All-cause mortality	No SGLT2i	709	37	
	SGLT2i	709	14	0.50 (0.27–0.95)
	No DAPA	354	13	
	DAPA	354	7	0.66 (0.25–1.72)
MMRM analysis	*Propensity-matched cohort*	*eGFR slope (standard error)*	*Treatment effect (95% CI)*	*p-value*
eGFR slope (mL/min/1.73m^2/year)	No SGLT2i	–0.91 (0.26)		
	SGLT2i	+0.87 (0.37)	+1.78 (0.87–2.69)	0.00013
	No DAPA	–1.04 (0.37)		
	DAPA	+1.24 (0.54)	+2.28 (1.01–3.54)	0.0004

*MACE: a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke.
DAPA=dapagliflozin

Another glucose-lowering drug category, the GLP-1 receptor agonists, have been recently demonstrated to possess CV and renal benefits in high-risk patients. Two members of this class, in contrast, were found to have a neutral effect on the heart, specifically lixisenatide and once-weekly, sustained release exenatide. The reason for this dichotomy is unclear but could reflect true differences in the drugs or potentially study methodology. Clegg *et al.* from the US and Europe, however, took an interesting opportunity from EXSCEL, the generally neutral exanatide CV outcome trial, to confirm the potential intrinsic benefits of SGLT2 inhibition on both cardiac and renal outcomes (abstract 130-LB). In this trial, which involved some 14,000 patients randomized to placebo or weekly exenatide on top of standard-of-care, about 10% were prescribed an SGLT2 inhibitor during the trial, with about 50% of these given dapagliflozin. The associations between prevalent SGLT2 inhibitor use and MACE, all-cause mortality, and eGFR were analyzed in the placebo group (Table 6). Using propensity-matching, based on clinical characteristics prior to initiation of SGLT2 inhibition, two cohorts of 709 patients were generated, one taking and one not taking SGLT2 inhibitors. Subsequent time-to-first adjudicated MACE and all-cause mortality were compared using Cox regression and changes in eGFR over time were also quantified using the Mixed-Effect Model Repeated Measure (MMRM) approach. Therapy with any SGLT2 inhibitor as well as dapagliflozin* specifically was associated with a numerical decrease in the HR for MACE and all-cause mortality as well as a more advantageous changes in the slope of decline in eGFR. Due to small numbers, most of the results did not achieve statistical significance, but were directionally concordant with data from the clinical trials (EMPA-REG OUTCOME, CANVAS) and the observational data sets (CVD-Real). This post-hoc analysis of EXSCEL appears to support the CV and renal benefits of the class, and also suggests that the benefits of empagliflozin and canagliflozin* may extend to dapagliflozin.* Notable, the large dapagliflozin CV outcome trial DECLARE will be completed this year.

Table 7. Comparative CV Risk of SGLT2 Inhibitors vs. Liraglutide* in Patients with T2DM

Outcomes	*SGLT2i (n=17,203)*	*Liraglutide (n=17,203)*
Combined CV event (hospitalization for MI or stroke),		
n (IR per 1000 person-years)	96 (8.8)	94 (8.8)
Hazard Ratio (95% CI)	1.01 (0.76-1.34)	Ref.
Heart failure hospitalization,		
n (IR per 1000 person-years)	96 (8.8)	140 (13.1)
Hazard Ratio (95% CI)	0.68 (0.52-0.88)	Ref.
Expanded combined CV event (hospitalization for MI, stroke, unstable angina, or coronary revascularization)		
n (IR per 1000 person-years)	155 (14.3)	151 (14.1)
Hazard Ratio (95% CI)	1.01 (0.81-1.27)	Ref.
MI hospitalizations,		
n (IR per 1000 person-years)	62 (5.7)	60 (5.6)
Hazard ratio (95% CI)	1.02 (0.72-1.46)	Ref.
Stoke hospitalization,		
n (IR per 1000 per person-years)	36 (3.3)	35 (3.3)
Hazard ratio (95% CI)	1.01 (0.64-1.61)	Ref.

*Follow-up started on the day following treatment initiation and ended at the occurrence of a study outcome, insurance disenrollment, treatment switch/discontinuation, or end of study period, whichever came first.
CV=cardiovascular; T2DM=Type 2 diabetes.

There are no trials comparing the effects on CV outcomes from SGLT2 Inhibitors vs. GLP-1 agonists. Patorno and Boston colleagues examined a large commercial US health insurance database (2013-16) to assess the comparative CV events in Type 2 diabetes patients taking any SGLT2 inhibitor vs. liraglutide (abstract 1492-P). They also used propensity matching to balance over 100 baseline characteristics in the two groups. Hazard ratios of a composite CV outcome (comprised of hospitalization for myocardial infarction [MI], or stroke) and also hospitalization for heart failure (HHF) were then determined. Secondary outcomes included an expanded composite CV outcome (hospitalization for MI, stroke, unstable angina, or coronary revascularization) and, individually, MI or stroke hospitalization. Over 30 months, patients initiating therapy with an SGLT2i saw no significant difference in the risk of the primary or secondary CV composite outcome but did experience an approximate 30% decrease in the risk of HHF (HR=0.68 [0.52-0.88]), compared with liraglutide (Table 7). Subgroup analyses in patients with vs. without CV disease at baseline yielded consistent results. The study suggests that the overall CV effects of these two classes were largely similar but with better effects on heart failure outcomes with SGLT2 inhibitors. These data, while limited, are consistent with the results from clinical trials of the drugs individually vs. placebo.

These and other presentations this week underscored the importance of understanding both the benefits as well as the risks of this newer glucose-lowering drug class, which is having a major impact in our approach to managing Type 2 diabetes, particularly when CV and kidney disease are present.

Hypoglycemia: Consequences and Implications

The threat of dangerously low blood glucose in people with both Type 1 and Type 2 diabetes remains despite our more physiologic insulin formulations and improved glucose monitoring technology. Therefore, there remains extreme interest in the frequency of, consequences from, and strategies to prevent hypoglycemia. Dr. Stephen Davis from the University of Maryland, presented findings from several large epidemiological studies and randomized control trials, taking place in both inpatient and ambulatory settings, which report that patients with diabetes have an increased risk of cardiac and all-cause mortality following hypoglycemic events. Despite the strong association in multiple studies, we still don't know a lot about causality. Clearly, it is not ethical to induce severe hypoglycemia in study subjects in order to directly observe effects on the heart and determine the mechanism. The closest evidence in humans comes from a case report describing a 23 year-old man with Type 1 diabetes who was wearing a CGM during a time period in which he injected insulin, and subsequently had severe and sustained hypoglycemia to 10-15 mg/dL. He was later found 'dead-in-bed', and the autopsy confirmed normal cardiac anatomy. This syndrome has long suspected to be due to severe hypoglycemia but a direct connection has been difficult to demonstrate.

To identify a mechanism for how insulin-induced hypoglycemia may result in sudden death, Simon Fisher, MD, PhD from the University of Utah conducted studies in a mouse model using hypoglycemic insulin clamps in which glucose levels were decreased to 10-15 mg/dL for a sustained period, and cardiac activity was measured by ECG. The study clearly demonstrated that cardiac impairments occurred in a reliable sequence of increasing severity, as the duration of hypoglycemia was extended. This sequence began with abnormalities of ventricular repolarization, followed by dissociation of atrial and ventricular electrical activity, and concluding in ventricular tachycardia (VT) and fibrillation (VF). The specific ECG sequence is QTc prolongation, premature ventricular contractions, first- and second-degree heart block, marked bradycardia and high degree AV block, third-degree heart block, and finally VT and VF. Further investigations showed that this cardio-electric sequence was mediated by both CNS neuroglycopenia and a brisk sympathoadrenal response. Interestingly, mice that underwent recurrent hypoglycemia prior to the sustained hypoglycemia period had a significant decrease in mortality. So in an interesting twist, recurrent hypoglycemia is a risk factor for severe hypoglycemia but may also serve as protection from its potentially fatal consequences.

While severe hypoglycemia is most often associated with Type 1 diabetes, we know from the ACCORD, VADT, and ADVANCE trials that those with long-standing Type 2 diabetes are also at significant risk for subsequent CV events. Christensen and colleagues from Denmark enrolled 80 patients with Type 2 diabetes using basal-bolus insulin therapy (mean age 63±9, mean BMI 33±6 kg/m^2, and mean HbA1c 8.7%) to undergo CGM for 6 consecutive days (abstract 398-P). They found that 47.5% had at least one episode of hypoglycemia <70 mg/dL and 23.7% had at least one episode of more severe hypoglycemia <54 mg/dL. Importantly, participants with at least one episode of hypoglycemia had significantly lower C-peptide levels than those without (494±460 vs. 821±479 pmol/L, p=0.004). Low C-peptide levels were associated with increased glycemic variability as well as hypoglycemia. Munshi and colleagues from Boston had similar findings assessing CGM data from a 2-week period, with 22% (2 of 9) of patients with Type 2 diabetes (mean age 80±9, HbA1c 8.9%) having hypoglycemia ≤55 mg/dL for ≥20 minutes (abstract 405-P). Nocturnal episodes occurred in 11% (1 of 9). Not surprisingly, participants with Type 1 diabetes (mean age 70±4, HbA1c 8%) in their cohort had a much higher rate of overall hypoglycemia, 91% (21 of 23), and nocturnal hypoglycemia, 65% (15 of 23). While these numbers are not unexpected, they are very concerning. Older adults with Type 1 and Type 2 diabetes have a greater risk for falls and a high incidence of cognitive impairment, among other co-morbidities, that make them less capable of avoiding hypoglycemia and more vulnerable to its consequences.

Linda Gonder-Fredrickson PhD from the University of Virginia spoke about the personal repercussions of hypoglycemia, which many times is the silent burden of diabetes since it is so rarely talked about. Beyond the unpleasant symptoms, hypoglycemia also potentially results in social embarrassment, mental disruption, interpersonal conflict, in addition to the more recognized accidents and injuries, and even death. The threat of hypoglycemia meets all the criteria of a major stressor, including unpredictability, perceived or actual lack of control, requirement for a high level of vigilance, and potentially serious consequences. For children especially, the fear of hypoglycemia can be worse than the actual event. Both patients and family members experience this fear and anxiety. In fact, spouses or parents of someone with diabetes can report even greater fear than the patient. This has significant

consequences including marital conflict and sleep disturbances due to a need to remain hypervigilant. The chronic threat of hypoglycemia has strong personal, interpersonal, and family implications, and these can be underestimated. Discussion of these fears and impact on relationships is important.

Hypoglycemia remains a major impediment to diabetes care in those on insulin, including both Type 1 and Type 2 diabetes patients. Understanding its causes and complications will help us to design better preventive strategies.

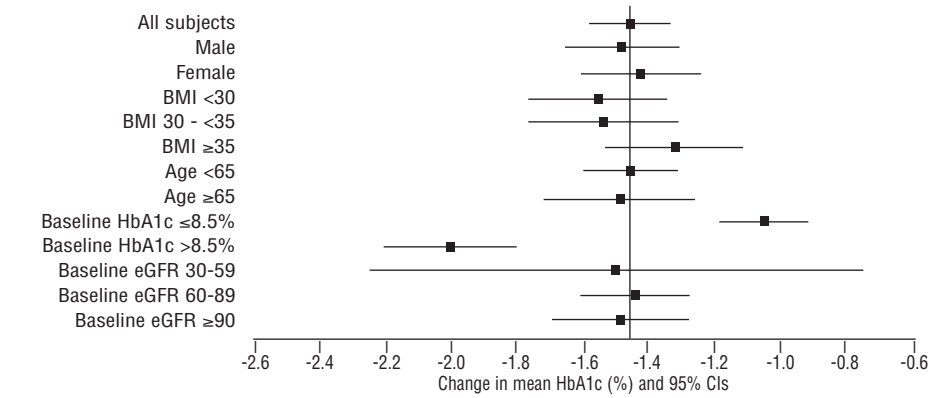
Incretin Inquiries

Incretin-enhancing drugs, the injectable glucagon-like peptide 1 (GLP-1) receptor agonists (RA's) and the oral dipeptidyl peptidase 4 inhibitors (DPP-4i's), have been commercially available for use in Type 2 diabetes for more than a decade. Yet, data concerning their use in diabetes management continues to evolve, including their potential role in Type 1 diabetes.

The *oral* formulation of semaglutide* was investigated as monotherapy in Type 2 diabetes in the PIONEER-1 trial by Aroda and international colleagues (abstract 2-LB). (The once-weekly *injectable* GLP-1 RA, semaglutide, has already been approved by the FDA as of last year.) In this randomized, double-blind, placebo-controlled Phase 3a trial, once-daily oral semaglutide was evaluated in treatment naïve patients (n=703) at three different doses (3, 7, and 14 mg). The primary endpoint was change in baseline HbA1c at week 26. All dosage strengths demonstrated a statistically significant treatment difference versus placebo for decrease in HbA1c from baseline (-0.6 [-0.8, -0.4] for 3 mg; -0.9 [-1.1, -0.6] for 7 mg; and -1.1 [-1.3, -0.9] for 14 mg; all $p<0.001$) and the 14 mg dose decreased body weight by -2.3 kg vs. placebo ($p<0.006$). As expected, nausea was the most common adverse event (5-16% with semaglutide, depending on dose, versus 6% with placebo). The oral formulation may one day be an alternative in the GLP-1 RA class especially for those patients averse to injectable therapy. Of course, whether this agent will possess the CV benefits of injectable semaglutide is not yet known.

Although the GLP-1 RAs are not approved for use in Type 1 patients,* research continues in this area. Dandona and co-investigators from New York and Nevada studied the addition of liraglutide to baseline insulin therapy in a relatively small group of patients with Type 1 diabetes (abstract 3-LB). In this 52-week randomized, double-blinded placebo-controlled trial, liraglutide 1.8 mg (n=26) was compared to placebo (n=20) in patients on insulin therapy for at least one year and who had no detectable plasma levels of C-peptide (mean BMI: 28.9 ± 1.4 kg/m^2; mean HbA1c: 7.8±0.2%, mean age: 46.7±1.9 years). Measures of placebo-adjusted HbA1c declined significantly in the liraglutide group at 52 weeks (-0.57±0.17%, $p=0.006$ vs. placebo) as did weekly adjusted average blood glucose (-15±4 mg/dL, $p=0.014$ vs. placebo). There were no changes in the incidence of hypoglycemia and time below 70 mg/dL based on CGM performed 4 weeks prior to and at the end of the treatment period. There were also no changes in insulin dose during the trial. Additionally, weight significantly decreased in the liraglutide group, as did systolic blood pressure.

Figure 6. Forest Plot of Change from Baseline HbA1c (%)—ITCA 650



Note: mITT = modified intent-to-treat populations (which consists of all treated subjects).
Note: The mean of the change from baseline is represented by a dot.
The line extending through the dot represents the 95% CI of the mean change from baseline.

Choice of GLP-1 RA often depends on cost/third party coverage, preference for device and administration schedule (daily versus weekly), and evidence of positive CV outcomes. Efficacy relative to glycemic control and body weight reduction between the GLP-1 RAs is often considered comparable. Pratley and co-researchers from the US, Europe, and India conducted a post-hoc analysis of the SUSTAIN-7 trial comparing HbA1c and body weight reductions in Type 2 diabetes receiving once-weekly subcutaneous doses of semaglutide 0.5 mg versus dulaglutide 0.75 mg, and semaglutide 1 mg versus dulaglutide 1.5 mg, relative to baseline HbA1c values (≤7.5%, 7.5-8%, 8-8.5%, 8.5-9%, and >9%) at 40 weeks (abstract 122-OR). Improvements in HbA1c and body weight were similar or favored semaglutide across all HbA1c subgroups (p-value for interaction: HbA1c $p=0.02$, body weight $p>0.05$). It is difficult to assert definitive efficacy advantages given the post-hoc design. However, semaglutide appears to provide similar, and in some instances greater, improvements in glycemic control and body weight reduction, regardless of baseline HbA1c, than dulaglutide.

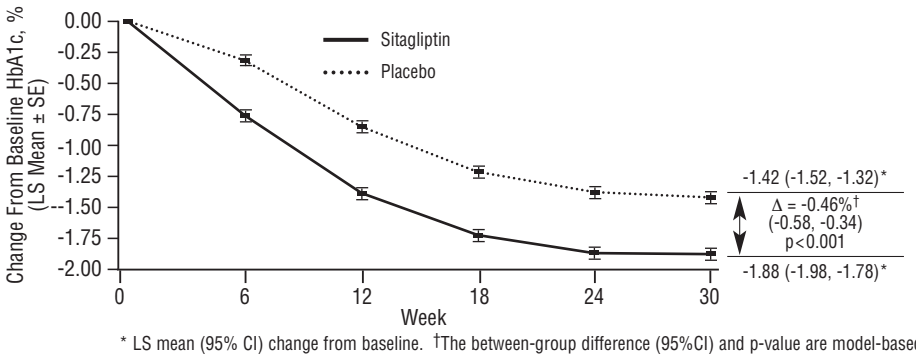
ITCA 650* is an investigational osmotic mini-pump designed to deliver a continuous infusion of the GLP-1 RA, exenatide, over a 3- or 6-month period. It is placed subdermally in the abdomen during an outpatient visit. Prabhakar *et al.* from Massachusetts and New Jersey assessed its efficacy as a function of baseline characteristics in a pooled subgroup analysis of Type 2 diabetes patients (abstract 1061-P). While patients with higher baseline HbA1c values generally had a superior response to ITCA 650, the agent demonstrated consistent responses across a wide variety of subgroups and is likely efficacious across a broad spectrum of patients with Type 2 diabetes (Figure 6).

In another investigation involving exenatide, data from the EXSCEL trial were evaluated to assess renal outcomes (eGFR, new macroalbuminuria, and two renal composites) from a pre-specified analysis plan (abstract 522-P). EXSCEL compared exenatide once-weekly subcutaneous administration versus placebo. Intention-to-treat analyses in 13,844 patients with baseline and at least one follow-up value showed no significant difference between eGFR levels with exenatide (LS mean +0.21 [-0.27, 0.70] mL/min/1.73 m^2, $p=0.39$). Cox regression was used to assess new macroalbuminuria, which occurred at similar rates (2.2% exenatide and 2.5% placebo, $p=0.19$).

The renal composite of 40% eGFR decline + renal replacement + renal death was not significantly different between groups, however, a second renal composite (40% eGFR decline + renal replacement + renal death + new macroalbuminuria) favored exenatide (HR 0.85, 95% CI: 0.73, 0.98; p=0.027). These data with exenatide are consistent with other members of this class (liraglutide, semaglutide), which have demonstrated renal benefits,* but mainly on macroalbuminuria, not actual decline in renal function. The implications of this for long-term kidney health are not clear.

Lastly, an investigation conducted by Roussel and colleagues from France, Spain, and the US assessed efficacy and safety of the DPP-4i, sitagliptin, in combination with insulin in Type 2 diabetes (abstract 112-LB). Patients who were inadequately controlled on metformin ≥1500 mg/day) and receiving dual or triple therapy with a DPP-4i and/or sulfonylurea were included. Patients already receiving metformin and sitagliptin (100 mg/day) were directly enrolled into the trial; all others were converted to metformin and sitagliptin during a run-in period and were stabilized. Patients (n=746) were then randomized to continuation of sitagliptin (+ metformin) or discontinuation of sitagliptin (placebo + metformin). Each group was initiated on basal insulin therapy (insulin glargine), which was titrated to fasting glucose. The primary endpoint after 30 weeks was change in HbA1c from baseline, with the sitagliptin continuation group demonstrating a statistically significant improvement (Figure 7). Additionally, those who continued on sitagliptin had a lower incidence of documented symptomatic hypoglycemia (glucose ≤70 mg/dL), with an event rate ratio of 0.73 (95% CI: 0.54, 0.98) and lower daily insulin requirements (-8.0 difference LS means [95% CI: -14.6, -1.5]) than those who had discontinued sitagliptin. From these data, the investigators concluded that continuation of sitagliptin in the setting of insulin initiation results in superior glycemic efficacy and less documented symptomatic hypoglycemia. Similar data have been reported with another DPP-4 inhibitor, linagliptin (Inzucchi *et al, Diabetes Obes Metab* 2015). The biological basis for this observation remains unclear but may relate to improved glucagon dynamics.

Figure 7. Change from Baseline HbA1c with Sitagliptin versus Placebo when Combined with Insulin Glargine and Metformin



* LS mean (95% CI) change from baseline. †The between-group difference (95%CI) and p-value are model-based.

Cystic Fibrosis-Related Diabetes

In a symposium entitled *Addressing Unique Challenges in Diabetes Management*, Dr. Toni Moran from the University of Minnesota discussed cystic fibrosis-related diabetes (CFRD). CF patients lose about 50% of their islet mass from 'neighborhood' inflammation and destruction of the exocrine pancreas, but that loss is typically not sufficient to result in diabetes. So, functional abnormalities in the islets must also be present, possibly related to genetic background, inflammation and endoplasmic reticulum stress, amyloid deposition, altered blood flow, or even an intrinsic beta cell defect related to the abnormal cystic fibrosis transmembrane conductance regulator (CFTR).

In young CF patients age 3-6, about 40% already have abnormal glucose tolerance, and they tend to develop CFRD early at puberty. More typically, it develops in the third decade of life. By age 40, more than 50% of CF patients have diabetes, a number that increases to 80% in the more severe CFTR genotypes. The main metabolic abnormality tends to be postprandial hyperglycemia. Diabetes is a predictor of mortality, as is weight loss in this population. Accordingly, the standard is to treat with insulin aggressively and early. Weight gain from insulin is actually a desired outcome.

CFRD is diagnosed with the same tools and thresholds we use to identify Type 2 diabetes (fasting glucose, HbA1c, and oral glucose tolerance test [OGTT]). Dr. Moran pointed out that an HbA1c <6.5% does not rule the condition, however. Current national guidelines are to test for CFRD annually using OGTT at least by age 10. In contrast to Type 2 diabetes, the diagnoses can be made during acute illness, so that hyperglycemia that persists beyond 48 hours during hospitalizations is considered enough evidence.

Treatment consists of maintaining optimal nutrition status, control of hyperglycemia, avoidance of hypoglycemia, and facilitating adaptation to living with CFRD. Specifically, insulin is viewed as an *anabolic* agent in this insulin-deficient condition and is typically dosed at about 0.5 units/kg/day. Depending on the dietary habits of the patient, it may be managed with mealtime short- or rapid-acting insulin or basal insulin. Some patients may need to progress to basal-bolus therapy. In contrast to typical recommendations for other forms of diabetes, the optimal diet in CF patients consists of high-calorie, high-fat, high-salt, with a new emphasis on nutritional quality as well. This should not change just because CFRD has developed. The goal is simply to give enough insulin to meet the metabolic demands, and hopefully lead to weight gain.

There are few data yet on the impact of diabetes therapy itself on clinical outcomes in CF patients. Thankfully, CFRD patients do not develop macrovascular disease and are at low risk even for microvascular disease.

There are no data yet to know whether earlier treatment in the pre-diabetic stage helps long-term outcomes. Ultimately, Dr. Moran speculated that newer therapies with corrector/potentiator therapies to fix the CFTR defect (perhaps even in utero) will likely prevent CFRD from even occurring.

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

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New ADA-EASD Consensus Report on T2DM Management

The ADA and EASD are in the process of revising their joint guidelines for the management of hyperglycemia in Type 2 diabetes. The last iteration of these, was published in 2015. It endorsed lifestyle change and metformin as initial therapy. Then, one of six additional medications was recommended, to be combined with metformin if needed for further glycemic lowering: a sulfonylurea, thiazolidinediones (TZD), DPP-4 inhibitor (i), SGLT2i, GLP-1 RA, or basal insulin.

Since 2015, however, there has been substantial new data from clinical trials about differential effects between drug classes on CV outcomes. Two classes, SGLT2i's and GLP-1 RAs, contain specific drugs with clear CV advantages. In fact, the ADA for the past two years has endorsed their preferential use in those with established CVD after metformin in their annually updated *Standards of Medical Care* document, published each January as a supplement to *Diabetes Care* (see Figure 8). With all these new data, however, the ADA and EASD felt it was time to revise their joint statement as a "Consensus Report."

A draft version of these recommendations was presented by members of the writing committee in a symposium on Tuesday morning. At the presentation, introductory comments were made by Dr. Melanie Davies of Leicester, UK, co-chair of the writing committee. The group undertook an extensive literature review and assembled their recommendations through two live meetings and biweekly teleconferences. Next, Dr. Judith Fradkin of the NIH and Dr. Apostolos Tsapas from Thessaloniki, Greece reminded the audience about "The Rationale and Importance of Antihyperglycemic Treatment." Well-known data from older clinical trials were reviewed, linking improved glucose control to reduced microvascular but not necessarily macrovascular events. The importance of patient-centered care was emphasized taking into account the prevention of complications and enhancement of quality of life. "Personalized Approach Based on Patient Characteristics and Comorbidities" was presented by Dr. Deborah

Table 8. Summary of Main Consensus Recommendations

- 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 and hypoglycemia, safety, tolerability, and cost.
- When injectable therapy is needed for glucose-lowering, GLP-1 receptor agonists (RA) should be considered as the first choice over insulin.
- 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 GLP1 RA, SGLT2i, or prandial insulin.
- Access, treatment cost, and insurance coverage should all be considered when selecting therapeutic strategies

Wexler of the Massachusetts General Hospital in Boston and Dr. Peter Rossing of the Steno Diabetes Center in Denmark. They reviewed the frequently coexisting comorbidities seen in individuals with diabetes, particularly CV and renal disease, and gave a first glimpse to the revised recommendations that use the presence or absence of CVD and heart failure as a major decision point in which drugs to prescribe. "Therapeutic Options" were discussed by Dr. Walter Kernan of Yale and Dr. Geltrude Mingrone of Rome, Italy. Here, the effects of exercise, various glucose-lowering drug classes, and bariatric surgery were reviewed and compared.

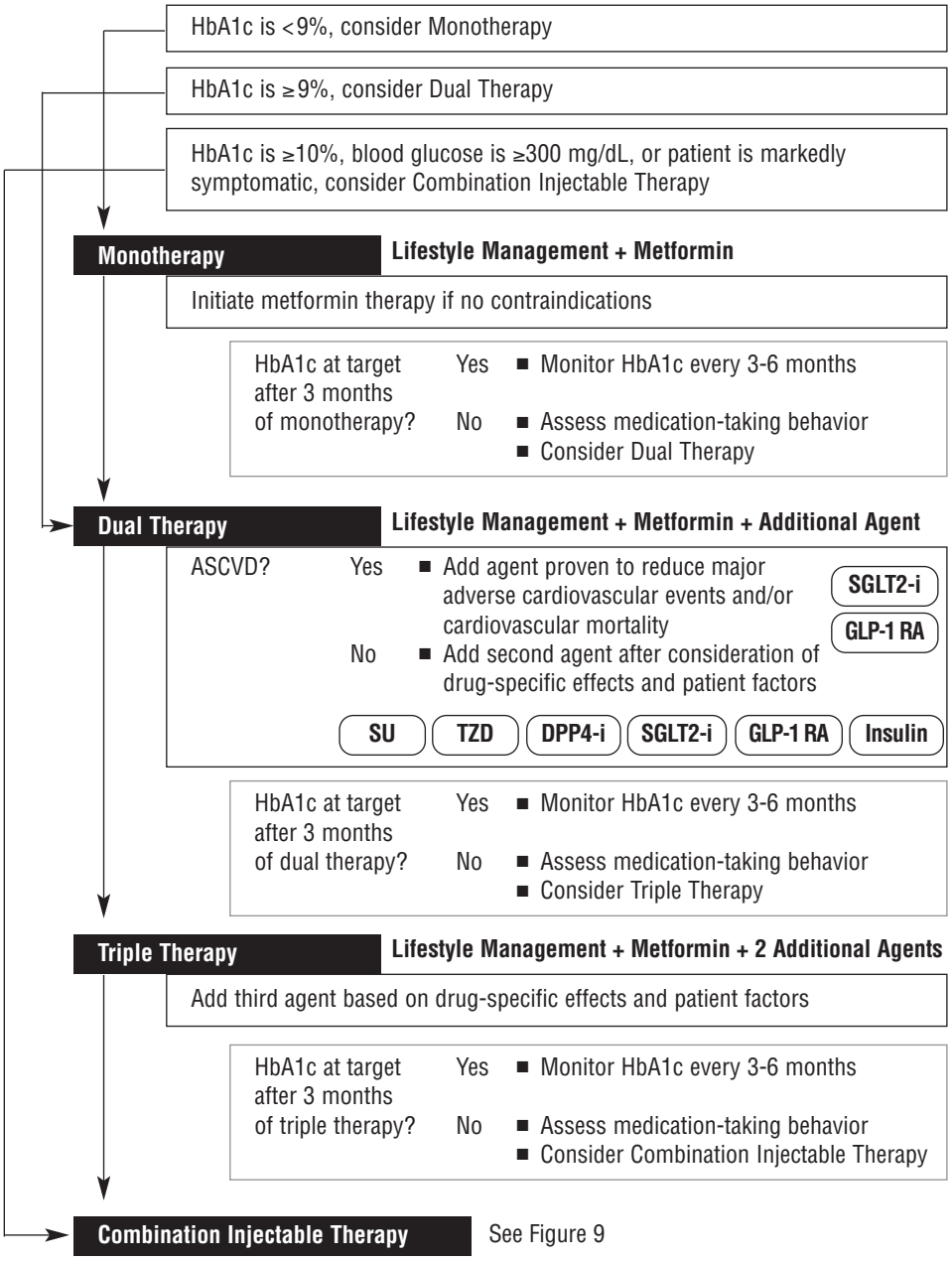
The next segment of the symposium was delivered by Dr. Dave D'Alessio of Duke University and Dr. Chantal Mathieu of Leuven, Belgium: "Strategies for Implementing Antihyperglycemic Therapy Plan." The draft version of the new algorithm was herein introduced. The committee's major consensus opinions are summarized in Table 8. The emphasis remains on patient-centered care, particularly as it relates to prevalent comorbidities, safety, patient preferences, and costs.

Lifestyle and metformin are still considered 'foundational therapy'; if additional glucose-lowering is required, the choice depends on the presence or absence of CVD. If present, then either a GLP-1 RA or SGLT2i should be used next, the latter being favored if heart failure predominates. The specific agent chosen should be a drug demonstrated to have CV benefits in large outcome trials. If CVD is absent, then the drug choice depends on issues related to weight, hypoglycemia, and cost, with prioritized recommendations based on individual characteristics for the six categories beyond metformin. For example, if weight loss (or the avoidance of weight gain) is key, the next step should be either an SGLT2i or a GLP-1 RA. If hypoglycemia is to be avoided, then either of these two or a DPP4i or TZD. If cost is paramount, then either a sulfonylurea or a TZD. One important change is the favoring of GLP-1 RAs over basal insulin in those patients who need to transition to injectable therapy, the former being viewed as a safer agent with equal efficacy.

Dr. John Buse, University of North Carolina and co-chair of the writing committee, finished the symposium with "Key Knowledge Gaps & Questions". The main issues raised pertained to the role of anti-obesity therapies; ways to preserve beta cell function; the still questionable role of metformin as initial therapy; whether the CV benefits of SGLT2i's and GLP-1 RAs will extend to lower risk patients; whether these drugs have added CV benefits when used in combination; the need for better insulin sensitizers and for better and safer insulins; and the lack of data on how to best manage Type 2 diabetes patients with fatty liver disease, the frail elderly, and adolescents.

We believe the writing committee has done an extraordinary job in synthesizing recent data and incorporating them into an outstanding consensus document. The public is invited to review the draft at https://professional.diabetes.org/2018EASDconsensus. Comments can be submitted to adacomments@diabetes.org until 11:59 PM EDT on Monday July 2, 2018.

Figure 8. ADA Standards of Medical Care, 2018; Antihyperglycemic Therapy in Adults with Type 2 Diabetes



Prioritizing Injectable Therapies

Choosing between various injectable agents for Type 2 diabetes was the subject of a Sunday morning symposium. Dr. Juan Frias, National Research Institute, California, led the session with his presentation, *Basal Insulin or GLP-1 Agonist—Which Agent First, When?* He stated that this question is likely considered by practitioners multiple times a day as patients demonstrate failure and lack of continued response to oral agents. Frias reminded the attendees that treatment should be individualized and, given the several options now available, we fortunately can address a number of metabolic defects with drugs' complementary mechanisms of action. He acknowledged that therapeutic inertia remains a concern with the average time to treatment with insulin being 7 years, if at all. With respect to medication choice, the following require consideration: efficacy, mechanism of action, hypoglycemia risk, potential for weight gain, CV effects, adverse event profile, ease of use, patient preference, and cost. Patient factors include: current HbA1c, age and general well-being, history of CVD, organ function, and socioeconomic factors.

There are multiple randomized controlled trials comparing the GLP-1 RAs to insulin that show comparable or better outcomes with the former. Frias discussed two in particular, GWAA and SUSTAIN-4, highlighting some early and relatively recent clinical data. Heine *et al.* on behalf of the GWAA Study Group (*Ann Intern Med* 2005) investigated exenatide twice daily versus insulin glargine in suboptimally controlled Type 2 diabetes patients. In this randomized, open-label, multinational 26-week trial, 550 patients (mean HbA1c 8.2% and 8.3% in exenatide and glargine patients, respectively, also receiving combination metformin and a sulfonylurea) were assessed for changes in HbA1c, fasting plasma glucose, body weight, 7-point self-monitored blood glucose, standardized test-meal challenge, safety, and tolerability. HbA1c changes were comparable; exenatide reduced postprandial glucose excursions greater than the insulin group, whereas fasting glucose was reduced to a greater degree by insulin glargine. Reductions in body weight favored the GLP-1 RA (treatment difference -4.1 kg) and rates of symptomatic hypoglycemia were comparable with a lower rate of nocturnal hypoglycemia observed with exenatide. Gastrointestinal-related adverse effects occurred at a higher rate in the exenatide group.

Multiple comparative investigations have occurred subsequent to this early trial with more rigorous study controls. Of note is the SUSTAIN-4 study, a randomized, open-label, parallel-group, multinational phase 3a trial that compared semaglutide once-weekly to insulin glargine, each for 30 weeks, as add-on therapy to metformin with or without sulfonylureas in insulin-naïve patients (Aroda *et al. Lancet Diabetes Endocrinology* 2017). The study found statistically significant differences in HbA1c reduction from baseline favoring both doses of semaglutide versus insulin glargine (estimated treatment difference for 0.5 mg dose of semaglutide: -0.38% [95 CI: -0.52 to -0.24] and for the 1 mg dose: -0.81% [95 CI: -0.96 to -0.67]). Mean reductions in body weight also favored the GLP-1 RA, ranging from -3.47 kg for the 0.5 mg dose and -5.17 kg with the 1 mg dose versus weight gain with insulin glargine of 1.15 kg (both $p<0.001$). Severe or blood-confirmed hypoglycemia occurred more frequently with insulin versus either semaglutide dose. As expected, the incidence of gastrointestinal side effects, nausea in particular, was far higher with semaglutide.

Several other research studies confirm what has now become common knowledge regarding GLP-1 RA therapies versus insulin glargine when added to oral agents. Overall, GLP-1 RAs provide more favorable reductions in HbA1c and body weight. Basal insulin is more effective in reducing fasting plasma glucose. A lower proportion of patients experience hypoglycemia with GLP-1 RAs versus insulin, including severe hypoglycemia. GLP-1 RAs result in lower systolic blood pressure, higher heart rate, and lower triglycerides and LDL-C compared with basal insulin. Finally, gastrointestinal side effects, especially nausea, occur with much greater frequency with GLP-1 RAs, leading to higher discontinuation rates than among those receiving basal insulin.

From his perspective, Frias would choose a GLP-1 RA over basal insulin unless there are known contraindications. Basal insulin would be an initial option if there are signs and symptoms of significant insulin insufficiency and/or contraindications/tolerability issues with GLP-1 RAs. He reminded the audience that many clinical trials and real world data demonstrate that control is not optimally achieved with either therapy and some patients may ultimately require both.

The second presenter, Helena Rodbard, MD, Rockville, Maryland, addressed the question, *Therapy Progression After Basal Insulin: GLP-1 RA vs. Prandial Insulin vs. Premixed Insulins?* These three options are identified in the ADA Standards of Medical Care in Diabetes—2018 (*Diabetes Care* 2018; 41 [Supplement 1]:S78; Figure 9). She, too, reminded participants that regardless of therapy choice, the issue of clinical inertia and long delays between initiation of basal insulin and treatment intensification is of significant concern. Rodbard shared some statistics from the recent analysis by Khunti *et al* (*Diabetes Obesity Metabolism* 2016) from 11,696 patients receiving basal insulin, underscoring the concerns both she and Dr. Frias share. The median time from treatment intensification following basal insulin initiation is 4.3 years. Of those considered eligible for intensification (HbA1c ≥7.5%), only 30.9% had therapy intensified and the average time to do so was 3.7 years.

Rodbard then reviewed the data for each therapeutic option beginning with the addition of a GLP-1 RA to basal insulin. The Get Goal-L trial (Riddle *et al. Diabetes Care* 2013) evaluated the addition of the short-acting GLP-1 RA, lixisenatide, in Type 2 patients inadequately controlled on basal insulin. After 24-weeks of lixisenatide versus placebo, the active therapy arm demonstrated a statistically significant improvement in HbA1c, weight loss, and reduction in basal insulin dose in comparison with placebo. Similarly, the AWARD-9 trial measured the effect of dulaglutide versus placebo when added to patients receiving insulin glargine over a 28-week period (Pazzilli *et al. Diabetes Obesity Metabolism* 2017). Results from this analysis demonstrated similar results to Get Goal-L in that HbA1c and weight reductions were significantly greater in the GLP-1 RA arm with no difference in hypoglycemia rates. Nausea, diarrhea, and vomiting were more common with dulaglutide.

With respect to choosing prandial insulin as a choice for intensification, results from the DUAL VII trial (Billings *et al. Diabetes Care* 2018) were shared. In this 26-week study (n=506), liraglutide was compared with insulin lispro, each combined with basal insulin degludec. The reduction in HbA1c values was comparable between groups. However, the liraglutide arm resulted in lower hypoglycemia rates and weight loss (versus weight gain).

Another option for initiation of prandial insulin is the sequential addition of meal time insulin versus the standard basal-bolus therapy (prandial given three times daily). This step-wise approach was evaluated in the FullSTEP Study (Rodbard *et al. Lancet Diabetes Endocrinology* 2014) over 32 weeks. One group of patients received one bolus of insulin aspart with the largest meal and additional doses added before the next largest meal at 11 weeks and 22 weeks if HbA1c did not fall below 7%. The comparator

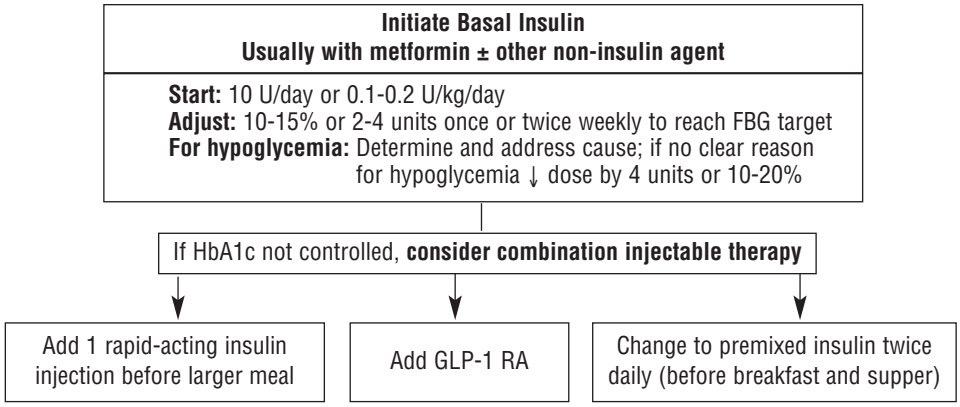
arm received traditional basal-bolus therapy with aspart doses three times daily prior to every meal. The results demonstrated comparable outcomes with respect to glycemic efficacy, yet lower rates of hypoglycemia and better patient satisfaction in the stepwise arm.

The third option, premixed insulins administered twice daily was discussed next. This option is simpler, but offers less flexibility. One investigation compared a co-formulation of insulin degludec and aspart administered twice daily* (not commercially available in the US) with the individual components (insulin degludec administered daily and aspart administered 2-4 times per day) given by separate injections. While non-inferiority was not confirmed, each strategy effectively improved glycemic control and there were no significant differences in hypoglycemia. Patient satisfaction scores related to social functioning were higher in the pre-mix treatment arm.

Dr. Rodbard concluded her presentation stating that intensification with GLP-1 RAs offers improved glycemic control, lower rates of hypoglycemia, and less weight gain. Progressive addition of rapid-acting insulin reduces HbA1c and reduces the risk of hypoglycemia relative to traditional basal-bolus dosing. Regimens with pre-mixed insulin lower HbA1c and are convenient.

Unfortunately, neither of the speakers adequately addressed cost. The GLP-1 RAs are amongst the most expensive of diabetes therapies. This needs to be incorporated as well into decision-making when choosing the best agent for the patient needing injectables. Branded insulin analogues are also extremely expensive, (see below) but versions of human insulin, including premixed formulations, can be obtained at much lower costs, and with proper education, used quite effectively.

Figure 9. Combination Injectable Therapy for Type 2 Diabetes (2018 ADA Guidelines)



Cost of In$ulin Therapy

Increasing prices for insulins, both human insulins and the newer analogs, have been a significant issue for patients and caregivers alike. Herkert and researchers from the Yale Diabetes Center administered a cross sectional survey to diabetes patients at the Center who were prescribed insulin (abstract 2-OR). The primary outcome was cost-related underuse of insulin within the past 12 months based on an affirmative response to any one of the following six questions: Did you ... (1) use less insulin than prescribed?; (2) try to stretch out your insulin?; (3) take smaller doses of insulin than prescribed?; (4) stop insulin?; (5) not fill an insulin prescription?; and (6) not start insulin ... because of cost? Using logistic regression controlling for age, gender, duration of diabetes, and income, the association between cost-related underuse and HbA1c >9% was evaluated. More than one-half of patients (199/354) completed the survey and respondents were equally distributed by gender (50.8% female), 60.8% white, and 41.7% with Type 1 diabetes. One-quarter (25.5%) of patients completing the survey reported cost-related insulin underuse and this was associated with lower income levels, variable drug coverage, and under-employment. Of significance was a 3-fold higher odds of HbA1c >9% (p=0.03) in patients who reported cost-related insulin underuse. Given the results of this survey, both the level of cost-related underuse (25.5%) and its association with poor glycemic control, the investigators concluded there is an urgent need to address rising insulin costs in the US.

In a related study, Luo and co-investigators from Massachusetts and California evaluated the impact, both clinical and economic, of a conversion program initiated by Medicare Advantage, switching beneficiaries with Type 2 diabetes from analog to human insulin (abstract 4-OR). The primary endpoints were mean HbA1c, rates of severe hypo- or hyperglycemic events, and risk of reaching the Part D coverage gap. Members (n=14,635; mean age 72.5 years) from 4 states (CA, AZ, NV, VA) were analyzed using interrupted time series and segmented regression with cut points at the beginning and end of 2015. A total of 221,866 insulin prescriptions were filled during this time period and the conversion decreased the proportion of analog insulins dispensed from 90% to 30%. Baseline mean HbA1c was 8.5% and had been on the decline in the previous year. At the start of the conversion program, the level of change in HbA1c was +0.14% (p<0.01) with a slope change of 0.02% (p<0.01). There were no significant changes in hypo- or hyperglycemia rates during the intervention and post-intervention periods. Moving to human insulins reduced the risk of reaching the coverage gap (HR 0.45, nominal 95% CI, 0.43-0.48, p<0.001).

In summary, utilizing human insulins versus analog insulins had no impact on rates of hospitalization for hypoglycemia or hyperglycemia and reduced the risk of reaching the coverage gap. However, the conversion did result in a slight increase in HbA1c values, the clinical relevance of which is unknown. Human insulins are generally more favorable with respect to cost (in some circumstances 10-times less than analogues) and their use is one mechanism to decrease the economic burden on patients.

The concern over skyrocketing insulin costs prompted the ADA Board of Directors to form an "Insulin Access and Affordability Working Group" in the spring of 2017. Their recommendations are presented in a recent publication of *Diabetes Care* (Cefalu WT, *et al., Diabetes Care* 2018; 41(6): 1299-1311).

Renal Rounds

NHANES data (2009-2014) suggest that 25% of US adults with diabetes have CKD (defined as eGFR <60 mL/min/1.73m^2 or albumin-to-creatinine ratio [ACR] ≥30 mg/g). CKD is a known risk factor for MACE, all-cause mortality, and hypoglycemia. Many presentations this week had a CKD focus, two of which are discussed below.

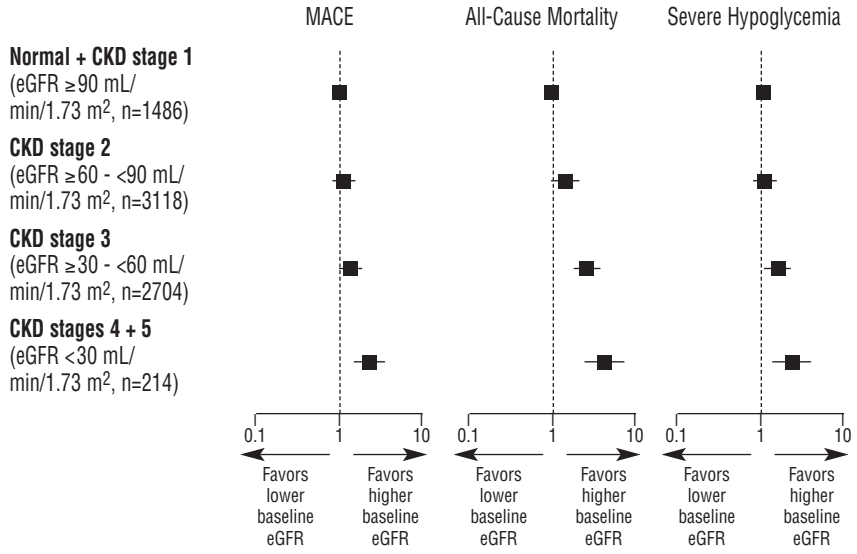
Amod and multinational coworkers conducted a secondary, pooled analysis from DEVOTE, examining whether baseline CKD stages were associated with an increased risk of MACE, all-cause mortality, or severe hypoglycemia in Type 2 diabetes patients (abstract 530-P). DEVOTE was a treat-to-target, randomized, double-blind study of 7,637 patients with Type 2 diabetes at high CV risk, treated once daily with insulin degludec or insulin glargine. The distribution of CKD stages at baseline were: normal + CKD stage 1, n=1486; stage 2, n=3118; stage 3, n=2704; and, stages 4+5, n=214.

Risks of MACE and all-cause mortality were significantly higher ($p<0.05$) in those with a higher baseline CKD stage (Figure 10), as was the incidence of severe hypoglycemia. Comparisons between treatment groups by CKD stage mirrored those from the primary analyses.

Cressman and associates from the US and UK utilized a clinical laboratory database to assess CKD prevalence and classified risk (low, moderate, high, or very high) based on KDIGO (Kidney Disease: Improving Global Outcomes) criteria (abstract 544-P). The population included 48,036 adults with Type 1 diabetes and 1,461,915 with Type 2 diabetes recently evaluated in US clinical practices and had both an ACR and eGFR between August 2014 and August 2017. Rates of eGFR decline were calculated for patients with >3 eGFR results over at least a 1-year period.

CKD prevalence was higher among the patients with Type 2 diabetes (44.3% vs. 31.6% of Type 1; $p<0.001$), as was the proportion classified as high or very high risk (17.8% vs. 12.0% of Type 1, $p<0.001$). Macroalbuminuria (ACR >300 mg/g) was uncommon (Type 1: 7.8%, Type 2: 8.3%); the majority with macroalbuminuria had an eGFR ≥60 mL/min (Type 1: 60%, Type 2: 53%). Median eGFR decline (mL/min/year) was low in the entire population (Type 1: -0.6, Type 2: -0.8), and in patients with ACR <30 mg/g (Type 1: -0.34, Type 2: -0.47) or ACR 30-300 mg/g (Type 1: -0.97, Type 2: - 1.06). However, median annual rate of eGFR decline in patients with macroalbuminuria was greater in those with Type 1 diabetes (-3.80 vs. -3.58 in Type 2 diabetes).

Figure 10. Effect of Baseline CKD Stages on Risk of MACE, All-Cause Mortality, and Severe Hypoglycemia in Patients with T2DM



CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; MACE=major adverse; T2D=type 2 diabetes.

Note: CKD stage comparisons (normal + CKD stage 1 as reference) Hazard ratios (95% CI)

Next-Gen CGMs

CGM is becoming a staple of glycemic management, at least in patients with Type 1 diabetes, and the technology is not stopping at external wearable devices. Several presentations this week focused on new ways to monitor glucose.

Ioacara and colleagues from Romania and the US showed data on the improved longevity of an implantable CGM system (abstract 901-P). Thirty-four participants with Type 1 diabetes (mean age 30±8 years, BMI 24±4 kg/m^2) had a sensor (Eversense, Senseonics, Maryland, US) inserted into their upper arm, with sensor assessments every 30-60 days for longevity, safety, and effectiveness. Survival analysis at post-implant days 90, 120, 150, 180, and 250 showed an estimated probability of sensor survival of 97%, 94%, 84%, 80%, and 51%, respectively. No insertion, removal, or device-related serious adverse events were reported.

In late 2017, the FDA approved the FreeStyle Libre Flash CGM System, which was in part an improvement over current CGMs in that calibration using a blood sample from a fingerstick is not necessary. The system uses a small sensor wire inserted below the skin's surface that continuously measures and monitors glucose. Users can determine glucose levels by waving a dedicated, mobile reader above the sensor wire to determine the current interstitial glucose level. The sensor can be worn for up to 10 days. Of note, this sensor does not provide real-time alerts or alarms in the absence of a user-initiated action. So, it cannot be used to avoid hypoglycemia during sleep, an important difference from the current CGM's. Also there have been some concerns about accuracy in the low ranges.

Seibold and colleagues from Germany and the United Kingdom reported on the impact of Flash CGM use on HbA1c in children, adolescents, and adults with either Type 1 or Type 2 diabetes (abstract 72-LB). A meta-analysis was conducted from data amalgamated from 17 studies reporting longitudinal HbA1c values from a total of 1338 participants (Type 1, n=1112; Type 2, n=226). Overall mean change in HbA1c was -0.56 (95% CI -0.76, -0.36), although there was substantial heterogeneity between trials (I^2=93%). Based on a further analysis, this heterogeneity was not thought to be due to the length of study, type of diabetes, or age of participant (children versus adult).

The use of novel forms of glucose monitoring is now a reality. While further optimization and cost effectiveness reports are needed, these updates are promising for our patients.

Kudos to our friend and colleague, **Gerald I. Shulman, MD, PhD** of Yale University who is the recipient of the 2018 Banting Medal for Scientific Achievement, the American Diabetes Association's highest honor. This medal recognizes significant and long-term contributions to the understanding, treatment, or prevention of diabetes. Dr. Shulman's Banting Lecture, delivered on Sunday, was entitled, "Mechanisms of Insulin Resistance: Implications for Obesity, Lipodystrophy, and Type 2 Diabetes," in which he described his decades of ground-breaking work in elucidating the pathophysiology of insulin resistance and Type 2 diabetes.

So Many Posters, So Little Time....

PCSK9 Effects in Diabetes

In the ODYSSEY OUTCOMES trial, Ray and multinational co-investigators randomly assigned 18,924 patients with recent acute coronary syndrome (ACS) and LDL-C ≥70 mg/dL on a maximum-tolerated dose of atorvastatin or rosuvastatin to alirocumab (a fully human monoclonal antibody to PCSK9) 75 mg or placebo administered SC every 2 weeks (abstract 6-LB). The dose of active drug was increased, in a blinded fashion, to 150 mg or decreased to placebo to achieve an LDL-C of 25-50 mg/dL.

Over a median follow-up of 34 months, alirocumab reduced time to first MACE, the primary endpoint, by 15% in the cohort including all patients, with effect similar across subgroups defined by baseline glucometabolic status (Table 9). New-onset diabetes was not increased with the PCSK9 inhibitor, as has been reported with statins.

Table 9. Time to First MACE by Glucometabolic Status

Category	*n (%) of Cohort*	*MACE Cumulative Incidence Alirocumab*	*Placebo*	*ARR*	*HR (95% CI)*
All patients	18,924	903/9462 (9.5)	1052/9462 (11.1)	1.6	0.85 (0.78, 0.93)
Diabetes	5444 (28.8)	380/2693 (14.1)	452/2751 (16.4)	2.3	0.84 (0.74, 0.97)
Prediabetes	8246 (43.6)	331/4130 (8.0)	380/4116 (9.2)	1.2	0.86 (0.74, 1.00)
Normoglycemia	5234 (27.7)	192/2639 (7.3)	220/2595 (8.5)	1.2	0.85 (0.70, 1.03)

ARR = absolute risk reduction.

Triple Therapy from the Start?

Abdul-Ghani and coworkers from Texas and Massachusetts reported 6-year follow-up data from the EDICT Study, a randomized open-label study in which newly diagnosed drug-naïve Type 2 diabetes patients were randomized to receive triple therapy (metformin/pioglitazone/exenatide, n=132) or an escalating dose of metformin followed by sequential addition of glipizide and then glargine insulin (conventional therapy, n=146) to maintain HbA1c< 6.5% (abstract 123-OR). Patients receiving triple therapy experienced significantly greater reduction in HbA1c after a mean follow-up of 6 years vs. conventional therapy (5.8% vs. 6.7%, p<0.001). Furthermore, progression of carotid IMT* (read blindly) was reduced by >50% (p<0.001) in triple therapy vs. insulin therapy. This group has been promoting triple therapy at diagnosis in Type 2 diabetes, but this approach has not caught on, mainly due to concerns about side effects, costs, and also the uncertainty about the need for such tight control in most older patients with Type 2 diabetes. However, as their data accumulate and show such positive effects, combined therapy is looking more attractive. Larger studies are needed and newer agents should also be tested.

Diabetes Mellitus Following Immune Checkpoint Inhibitor Therapy for Cancer

Immune checkpoint inhibitors (ICI) (e.g., anti-PD-1, anti-PD-L1, and anti-CTLA-4), which are increasingly being used to treat solid tumor malignancies, can cause immune-related adverse events (irAE). Mizokami-Stout *et al.* from the US and China reported on 51 cases of diabetes-related irAEs that they identified during a literature review (abstract 204-LB). Thirty-five patients presented in DKA (21 with Type 1 diabetes), 15 with hyperglycemia, and 1 with lab data not reported. The median age of the 31 males and 20 females was 63 years. Median time to onset of diabetes was 7 weeks after treatment initiation. Anti-GAD65, IA2, or ZnT8 were positive in 53% and negative or not reported in 47%. The two most common cancers treated were melanoma (n=23) and non-small cell lung cancer (n=11). The majority were treated with ICI monotherapy: anti-PD-I (n=34); anti-PD-L1 (n=4); anti-PD-1 + CTLA-4 (n=7); and anti-CTLA-4 then anti-PD-1 (n=6). For the 28 cases with data, ICI was stopped in 16 and continued in 12 upon diagnosis of diabetes. At onset, 3 cases with known Type 2 diabetes continued with oral meds, but all were treated with insulin and fluids. Thirty-eight patients remained insulin-dependent, 1 stopped insulin 81 days after ICI was discontinued; and, no data were reported for 12.

We are seeing such cases at our institution as well, in addition to ICI-induced thyroiditis and hypophysitis. Oncologists should have a high level of suspicion about these adverse events when their patients taking drugs in these categories present with symptoms suggestive of endocrine or metabolic disease. When they occur, endocrinologists and oncologists should collaborate in managing such patients.

** 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 37*

The post-test and evaluation must be completed on-line (not by US mail or fax) at https://goo.gl/XWW7KT.

1. 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

2. Which of the following is NOT true about metformin for treatment of Type 2 diabetes?
   a. Metformin is considered first-line pharmacotherapy in Type 2 diabetes.
   b. Metformin may confer cardiovascular benefit in Type 2 diabetes.
   c. Metformin is renoprotective in Type 2 diabetes.
   d. Metformin is available generically and inexpensive in comparison with other pharmacotherapies.

3. Professional clinical glucose monitoring (CGM), when a practice owns CGM devices and uses in multiple patients, is a billable service.
   a. True
   b. False

4. Which of the following best describes monogenic diabetes?
   a. Monogenic diabetes is commonly under-diagnosed, occurring in 1-5 % of all patients with diabetes.
   b. Classical features include: onset < 35 years, parental history of diabetes, and negative islet cell antibodies.
   c. When diagnosed in adolescents, monogenic diabetes is termed Maturity Onset Diabetes of the Young (MODY).
   d. all of the above

5. Which of the following medications improves the metabolic parameters: HbA1c AND 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)

6. There is little support by national diabetes organizations to standardize reporting of CGM, often referred to as the Ambulatory Glucose Profile (AGP).
   a. True
   b. False

7. FIB-4, a simple calculation based on mostly routine laboratory measures, is an inexpensive method that may assist in identifying Type 2 diabetes patients at risk of adverse liver outcomes.
   a. True
   b. False

8. Which statement is true based on current clinical evidence:
   a. Canagliflozin decreases the risk of CV mortality, ***and*** hospitalization for heart failure (HHF), ***and*** is renoprotective.
   b. Dapagliflozin decreases the risk of CV mortality, ***and*** HHF, ***and*** is renoprotective.
   c. Empagliflozin decreases the risk of CV mortality, ***and*** HHF, ***and*** is renoprotective.

9. Peripheral neuropathy precedes the diagnosis of diabetes in many individuals, affecting approximately 1 in every 5 with prediabetes.
   a. True
   b. False

10. From animal models, an odd paradox is that recurrent hypoglycemia is a risk factor for severe hypoglycemia, but may also serve as protection from its potentially fatal consequences.
   a. True
   b. False

11. Fear of hypoglycemia is generally not a concern for patients with Type 2 diabetes as it is for those with Type 1 diabetes.
   a. True
   b. False

12. According to data presented this week, which of the following statements about the intersection between diabetes and chronic kidney disease is false?
   a. The prevalence of chronic kidney disease is higher in patients with Type 2 diabetes compared to Type 1 diabetes.
   b. Macroalbuminuria is common (prevalence >50%) among patients with diabetes.
   c. Most patients with macroalbuminuria have an eGFR ≥60 mL/min.
   d. Patients with diabetes and macroalbuminuria have a median annual decline in eGFR of ~4 mL/min.

13. Treatment of cystic fibrosis-related diabetes (CFRD) consists of maintaining optimal nutrition status, control of hypoglycemia, and the avoidance of insulin.
   a. True
   b. False

14. In the draft version of the updated ADA-EASD Consensus Report, choice of medication after metformin continues to include patient specific characteristics, with preferential use of select medications based on history of cardiovascular disease.
   a. True
   b. False

15. After lifestyle management and metformin, which of the following medications is NOT a standard consideration for dual therapy according to recent ADA-EASD guidelines?
   a. sulfonylureas
   b. thiazolidinediones
   c. GLP-1 receptors agonists
   d. meglitinides

16. Choice of dual injectable therapy (if HbA1c is uncontrolled), as recommended by the ADA-EASD proposed guidelines, includes:
   a. add 1 rapid-acting insulin injection before larger meal
   b. add GLP-1 RA
   c. change to premixed insulin twice daily (before breakfast and dinner)
   d. any of the above

17. Clinical inertia, the failure to intensify diabetes medication regimens in the setting of poor glycemic control, continues to be a significant issue in the care of diabetes patients.
   a. True
   b. False

18. While non-insulin therapies are generally quite expensive for patients, the cost of insulin products remains relatively inexpensive.
   a. True
   b. False

19. An advance in CGM technology, such as the FreeStyle Libre Flash™ system, is that blood samples from fingersticks are not necessary.
   a. True
   b. False

20. Based on recent clinical investigations, the risks of major adverse cardiovascular events (MACE), all-cause mortality, and severity hypoglycemia do ***not*** increase as chronic kidney disease worsens in patients with Type 2 diabetes.
   a. True
   b. False

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