Diabetes2017

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Important data on diabetes presented at the 77th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2017**, a newsletter CME program that is being offered to you by Yale School of Medicine. After receiving the newsletters by e-mail, please go to www.cme.yale.edu and take the CME quiz. You will qualify for up to 5.0 *AMA PRA Category 1 Credits™* to be issued by Yale School of Medicine.

Diabetes 2017 is being offered to physicians practicing in the United States. After successfully completing this program, participants 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.

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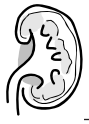
SGLT-2 Inhibitors, CVD & CKD: Class Effect?

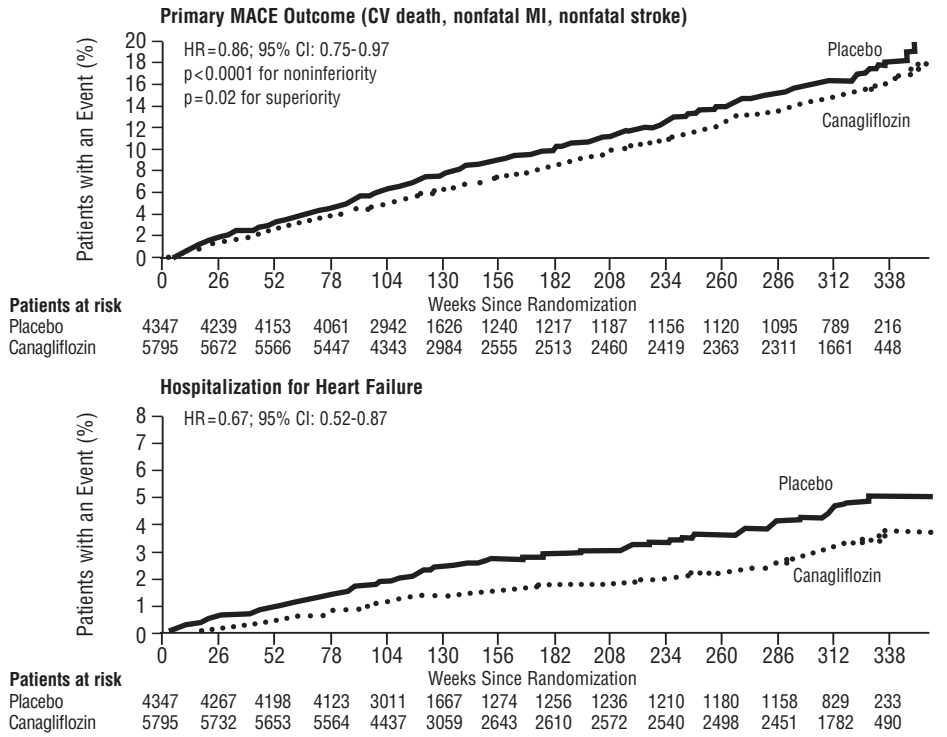


In front of a standing-room-only crowd at the San Diego Convention Center, the long-anticipated results of the Canagliflozin Cardiovascular Assessment Study (CANVAS) program were revealed on Monday afternoon. This was the first time that cardiovascular (CV) outcome data from a large, randomized clinical trial involving an SGLT-2 inhibitor (i) were presented since the EMPA-REG OUTCOME trial in 2015. That SGLT-2i study was associated with a 14% reduction in major adverse CV events (MACE), driven by a surprising 38% reduction in CV mortality. Subsequent publications have revealed reductions of 35% in hospitalization for heart failure and 39% in progression of nephropathy. The two key questions buzzing through the audience prior to the presentation were:

(1) Will the benefits seen in EMPA-REG now be considered a "class effect?", and
(2) Might the benefits seen in EMPA-REG apply to a primary prevention population?

Canagliflozin was the first SGLT-2i available in the US and is currently the most commonly prescribed member of this class. All SGLT-2 inhibitors reduce HbA1c on the order of 0.6-0.8% and have modest benefits on blood pressure (-4/2 mmHg) and body weight (-2 kg). Other potential benefits include a small decrease in triglycerides and significant reductions in urinary albumin excretion. Two concerns raised specifically with canagliflozin are small increases in bone fractures and lower extremity amputations. The latter has recently led to a 'black-box' warning from the FDA.

Figure 1. Major Adverse CV Events and Heart Failure Hospitalizations in CANVAS and CANVAS-R



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SGLT-2 Inhibitors, CVD & CKD: Class Effect?

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In this context, the symposium began. Background was provided by Dr. Gregory Fulcher of the University of Sydney, Australia. He described the landscape of Type 2 diabetes therapy and regulatory concerns about the potential impact of glucose-lowering medications on CV risk. Indeed, CANVAS emerged as one of the first new-generation CV outcome trials, in response to the FDA Guidance that mandated large trials of this nature to ensure that there is no CV risk imposed by new therapies. The CANVAS program consisted of two trials that were analyzed together, CANVAS and CANVAS-R, the latter initially assembled to focus on renal endpoints as well.

Ken Mahaffey of Stanford University, California reviewed the study methods. Inclusion criteria were identical for both trials. Patients had to have Type 2 diabetes with HbA1c of 7.0-10.5% and be at least 30 years old with a preexisting history of symptomatic atherosclerotic cardiovascular disease (CVD), or have two or more CVD risk factors and be at least 50 years of age. Based on the mechanism of action of the drug, an eGFR of more than 30 ml/min/1.73 m^2 was also necessary. In all, 10,142 patients were enrolled into the program (4330 in CANVAS and 5812 in CANVAS-R) and they were followed for a mean of 188 weeks. The patients were randomized to canagliflozin (forced titrated to 300 mg in CANVAS and titrated if needed for glycemic control in CANVAS-R) or placebo. 96% of patients completed the study and vital status was known in 99.6%. About 30% of patients stopped their assigned therapy in both groups.

Baseline characteristics included mean age 63.3 years, with about 65% being male. The mean duration of diabetes was 13.5 years and nearly two-thirds had a history of established CVD. The baseline HbA1c was 8.2%.

Dr. Bruce Neal of the Georges Institute in Australia, study co-principal investigator, presented the intermediate and CV outcomes. The canagliflozin group experienced a mean 0.58% reduction in HbA1c compared to placebo. There were also modest reductions in body weight (-1.6 kg) and systolic blood pressure (3.9 mmHg) (all $p<0.001$). Since investigators were asked to treat all patients to prevailing HbA1c targets, more participants in the placebo group had other glucose-lowering agents added to their regimen during the study. The primary MACE endpoint was reduced in the canagliflozin arm as compared to placebo (26.9 vs. 31.5/1000 patient-years) for a hazard ratio (HR) of 0.86 (95% CI: 0.75-0.97; $p<0.0001$ for noninferiority; $p=0.02$ for superiority) (Figure 1). None of the individual components of MACE, however, met the test for statistical significance (Figure 2). The HR for all-cause mortality was 0.87 (95% CI: 0.74-1.01). Hospitalization for heart failure was significantly reduced, however (HR 0.67 [0.52-0.87]). The CV results were consistent across a variety of pre-specified subgroups with one exception—those already on diuretics appeared to benefit to a greater degree than those without ($p<0.001$ for interaction). In addition, we note that the primary prevention cohort (i.e., age >60 years and risk factors but no overt CVD) appeared not to benefit from the study drug with an HR of 0.98 (0.74-1.30), although the statistical test of heterogeneity was only 0.18, so non-significant for interaction.

Dr. Dick de Zeeuw of University of Gronigen, The Netherlands presented the renal outcomes. Progression of albuminuria occurred less frequently in the canagliflozin arm (HR 0.73 [0.67-0.79]). The prespecified composite "hard" renal outcome, which was comprised of sustained 40% reduction in eGFR, the need for renal replacement therapy, or renal death also favored the canagliflozin-treated patients (HR 0.60 [0.47-0.77]) (Figure 3).

Safety outcomes were discussed by Dr. Vlado Perkovic of Georges Institute, Sydney, Australia. In addition to the increased risk of genital mycotic infections, there were two significant findings. The first was an increased risk of amputation (6.3 vs. 3.4/1000 patient-years) corresponding to a HR of 1.97 (95% CI: 1.41-2.75). Among the affected patients, 71% had their highest amputation at the level of the toe or metatarsal. The second was an increased risk of fractures (HR 1.26 [1.04-1.52]). There was heterogeneity in the fracture outcome, however, with the risk elevated in CANVAS (1.55), but not in CANVAS-R (0.86). DKA episodes were more frequent in the active therapy group but very small in number (0.6 vs. 0.3/1000 patient-years).

To conclude the session, study co-principal investigator, Dr. David Matthews of Oxford

Figure 2. Effects of Canagliflozin on Cardiovascular, Renal, and Other Outcomes in the CANVAS Program (n=10,142)

	Canagliflozin (n=5795) Event rate per 1000 patient-years	*Placebo (n=4347) Event rate per 1,000 patient-years*	*Hazard Ratio (95% CI)*
3-points MACE	26.9	31.5	0.86 (0.75-0.97)
CV mortality	11.6	12.8	0.87 (0.72-1.06)
Nonfatal MI	9.7	11.6	0.85 (0.69-1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71-1.15)
Fatal/nonfatal MI	11.7	12.6	0.93 (0.77-1.13)
Fatal/nonfatal stroke	8.0	9.9	0.85 (0.68-1.07)
All-cause hospitalization	118.7	131.1	0.94 (0.88-1.00)
HF hospitalization	5.5	8.7	0.67 (0.52-0.87)
All-cause mortality	17.3	19.5	0.87 (0.74-1.01)
Albuminuria progression	89.4	128.7	0.73 (0.67-0.79)
Renal composite*	5.5	9.0	0.60 (0.47-0.77)

*40% reduction in eGFR, renal replacement therapy, and renal death

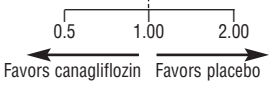
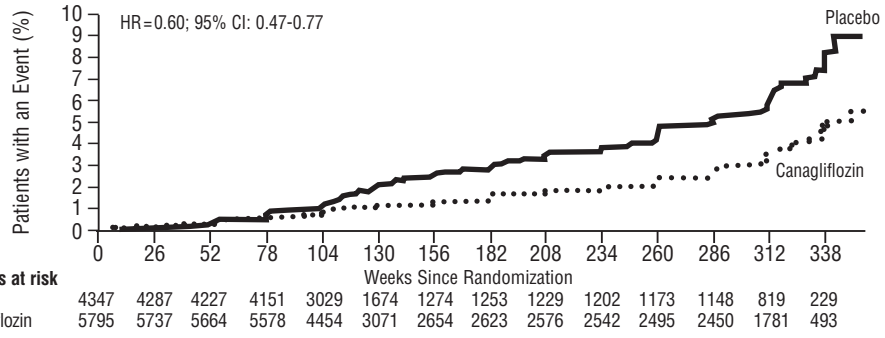


Figure 3. Renal Composite Outcome in CANVAS and CANVAS-R



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University, UK summarized the findings and provided some perspective. He contrasted the CANVAS results to those of EMPA-REG and suggested that the current study confirmed a class effect, while acknowledging that some of the primary composite outcome's components were variable between groups. He also suggested that since CANVAS recruited both those with and without CVD that the data supported an effect in primary prevention.

The independent commentary was provided by Professor Cliffort Bailey of University of Aston, UK, who congratulated the study team for a well-conducted trial and essentially supported Prof. Matthews' conclusions but pointed to concerns regarding the amputation and fracture adverse events.

Our view is that the CANVAS program results, in general, buttress those from EMPA-REG, confirming CV and renal benefits from this class of medication. There are some differences in terms of the MACE components between the drugs, but this may be the result of chance, study methodology, varying patient characteristics, or some inherent differences between the two drugs. As for the second important question about primary prevention, the CANVAS results indicate a CVD benefit in those participants with just risk factors, but not overt CVD. The new findings of an increase in amputations and fractures, which was not seen in EMPA-REG, are concerning however. How these findings will impact the use of canagliflozin moving forward remains to be seen.

Diabetes Care for Older Adults

In a symposium entitled, *Diabetes Care for Older Adults*, experts from around the world discussed this increasingly important aspect of medicine. Graydon Meneilly, MD from Vancouver, British Columbia began the symposium addressing the notion of frailty, a multidimensional syndrome that gives rise to increased vulnerability in the aged. A mildly frail individual, for example, is one who needs help with high-level activities of daily living (ADL) such as paying bills, but is otherwise able to perform other ADLs independently. A severely frail individual is one who is completely dependent on others for all ADLs. The median life expectancy of a severely frail individual is 30 months, and further decreased to 23 months for those with diabetes. CV risk factor targets are necessarily reduced in this group of patients, an acknowledgment of their limited life expectancy and propensity for drug-associated adverse effects. Table 1 outlines the moderated targets for HbA1c, blood pressure (BP), and LDL-C in older adults, as recommended by three diabetes organizations—Diabetes Canada, the American Diabetes Association, and the International Diabetes Federation.

Table 1. Diabetes Canada (DC), American Diabetes Association (ADA), and International Diabetes Federation (IDF) Targets for HbA1c, BP, and LDL-C in Older Adults

	DC	*ADA*		*IDF*	
BP	<130/80	Healthy	<140/90	Functional/independent	<140/90
		Complex/intermediate	<140/90	Frail	<150/90
		Very complex/poor health	<150/90		
LDL-C	≤80mg/dl	Statins unless contra-indicated or not tolerated			<80mg/dl
HbA1c	Healthy ≤7.0%	Healthy	<7.5%	Functional/independent	7.0-7.5%
	Frail ≤8.5%	Complex/intermediate	<8.0%	Functional/dependent	7.0-8.0%
		Very complex/poor health	<8.5%	Frail	<8.5%

Dr. Meneilly recognized the challenge for clinicians providing evidence-based diabetes care for the elderly population due to the paucity of studies that include them as participants.

In a study by Palta *et al.* (*Diabetes Care*, 2017) analyzing data from adults ≥65 years (n=7333) from the Third National Health and Nutrition Examination Survey (NHANES III) and their linked mortality data, it was concluded that an HbA1c of >8.0% was associated with increased risk of all-cause and cause-specific mortality in older adults with diabetes. On the other hand, a cross-sectional study of 1288 older adults (≥65 years) with diabetes, also from the NHANES from 2001 to 2010, suggested a significant degree of overtreatment of diabetes in older adults (Lipska *et al., Diabetes Care*, 2015). Approximately 62% of patients had HbA1c less than 7%; this proportion was similar across health categories—relatively healthy (62.8%), complex/intermediate health (63.0%), and complex/poor health (56.4%). Of those with HbA1c <7%, 54.9% were treated with either insulin or a sulfonylurea (with the proportion also being similar across health categories), placing them at risk for hypoglycemia. With insulin being second only to warfarin in terms of drug-related emergency department visits and hospitalizations, these data raise serious concerns.

Apart from declining cognitive function, which has been bidirectionally linked to hypoglycemia, Dr. Meneilly added that the elderly may have hypoglycemia unawareness due to reduced autonomic and neuroglycopenic symptoms, thereby placing them at higher risk for severe hypoglycemic events. He emphasized the need for education of patients and families/caregivers regarding the symptoms and perils of hypoglycemia, and highly recommended the use of agents not associated with hypoglycemia. Dr. Meneilly acknowledged that sulfonylureas, despite their risk for hypoglycemia, may often be utilized in situations when drug cost plays a significant role. In such cases, however, he strongly advised against the use of glyburide, which has been associated with higher incidences of hypoglycemia compared to others in its class.

He proceeded to discuss agents from the newer drug classes for diabetes including DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors, which may have a growing role in the management of older individuals since they do not result in hypoglycemia. Moreover, each has been studied extensively in those over the age of 65. The DPP-4 inhibitors are now considered neutral for CV events and are widely viewed as safe medications for the elderly. Dose reductions for elderly with declining renal function are usually necessary for most drugs in this class. The latter two drug categories have been demonstrated to have CV benefits, which is important in those with long-standing diabetes. However, SGLT-2 inhibitors may increase the risk of dehydration, which could result in falls, as well as genitourinary infections and acute kidney injury, so caution is advised.

Dr. Meneilly concluded his part of the symposium by reminding the audience to consider the functional status and comorbidities of the patient when determining targets for therapy, and reiterated the importance of avoiding hypoglycemia.

The second speaker, Jeffrey B. Halter, MD, a geriatrician from Ann Arbor, Michigan discussed CVD. There appears to be a significant age-related increase in acute myocardial infarction, especially in those individuals with diabetes. The risk for women is slightly lower than that of men, although after

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menopause the risk slowly converges. Dr. Halter discussed a proposed pathway that links aging, muscle, and risks for diabetes and CVD (Figure 4). As one ages, there is lower endurance and increased muscle wasting, resulting in decreased physical activity. This leads to lower energy expenditure, giving rise to increased obesity and specifically abdominal fat, along with increased insulin resistance. Ultimately, these risk factors can culminate in hypertension, Type 2 diabetes, and dyslipidemia, each of which augment the risk for CVD.

As for reversing this trend, a recent study by Villareal *et al.* (*NEJM*, 2017) demonstrated that combined aerobic and resistance exercise was the most effective means of improving functional status of obese, older adults compared to either form of exercise alone. Regarding medical therapy, Dr. Halter pointed to several studies suggesting that metformin use in the elderly has advantages over sulfonylureas, with few data comparing metformin to newer agents.

The third presenter, Dr. Susan Kirkman, Chapel Hill, NC described significant heterogeneity in older patients in terms of duration of diabetes, functional status, life expectancy, and comorbidities in patients of the same age. There is also substantial variation in the location these individuals live—home, assisted living, nursing home, rehabilitation unit, and acute care hospital. There are evolving challenges as patients decline in functional capacity and require transfer of care to different settings (Figure 5).

Dr. Kirkman went on to discuss the three well-known studies looking at intensive glycemic control and vascular complications in patients with diabetes: ACCORD, ADVANCE, and VADT. All studies demonstrated a decrease in microvascular complications with intensive glycemic control. ACCORD and ADVANCE did not show a correlation between glycemia control and CVD, whereas VADT revealed a minimal decrease in risk. ADVANCE and VADT did not show a correlation between intensive glycemic control and mortality, whereas the ACCORD trial was actually halted due to increased mortality in the more intensively controlled group. Severe hypoglycemia in older patients was seen in both arms of the trial. Importantly, unrecognized cognitive impairment predicted severe hypoglycemia; and, the increased mortality in the ACCORD trial largely occurred in those <65 years. While each of these studies included older patients, those who were frail or had recognized cognitive impairment were excluded. Interestingly, despite numerous studies reporting the danger of hypoglycemia, another study by Lipska and colleagues evaluating national trends in US hospital admissions of Medicare beneficiaries for diabetic emergencies revealed a marked decline in admissions for hyperglycemia, but no significant change in admissions for hypoglycemia (*JAMA*, 2014). This was despite increasing use of medications that do not promote hypoglycemia.

Are there some elderly patients who may still benefit from more stringent glucose control? Table 3 outlines patient characteristics that might drive such decision making.

Concepts in diabetes care are perpetually evolving. As our population ages and life expectancy increases, there arises a greater need for guidelines and targets tailored to older patients. Taking into account the patient's state of health and functional capacity in formulating goals and treatment plans is key to minimizing risks. Ultimately the guiding principle remains the same: first, do no harm.

Figure 4. Proposed Pathway Linking Aging, Muscle, and Risks for Diabetes and CVD

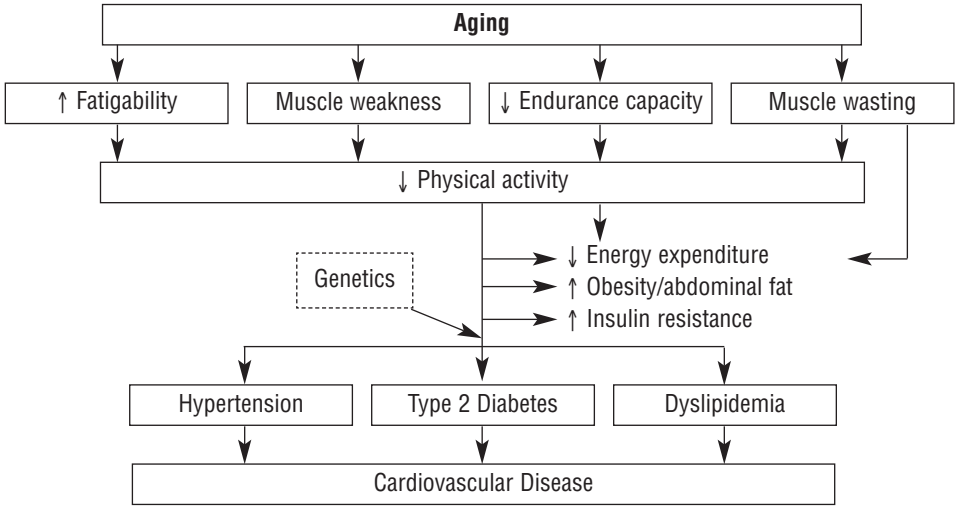
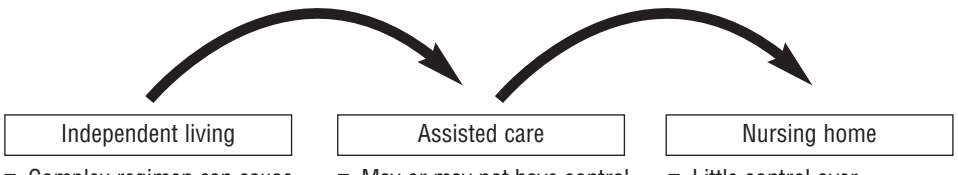


Table 3. Characteristics of Patients Who May Benefit or May be at Risk from Intensive Treatment of Glycemia

Who may benefit?	*Who is at risk?*
Younger patients	Old and frail patients
Short duration of diabetes mellitus	Long duration of diabetes
No micro-/macro-vascular disease	Presence of micro-/macro-vascular disease
Low comorbidity burden	Multiple comorbidities
Better overall health	Unable to follow regimen safely
Longer life expectancy	

Figure 5. Diabetes in the Aged: Management Challenges in Various Settings



Independent living	Assisted care	Nursing home
■ Complex regimen can cause harm if patient is unable to follow	■ May or may not have control over meal content	■ Little control over time/content of diet
■ Acute illness can decrease cognitive/physical status	■ Assistance with medications but not blood glucose monitoring or insulin	■ Higher risk of side effects with oral medications
■ Need regular education and re-evaluation	■ High risk of failure with acute illness	■ Higher risk of illness, dementia/depression
		■ Greater degree of dependence on staff for diabetes care

A Decade of Incretin-Based Therapy

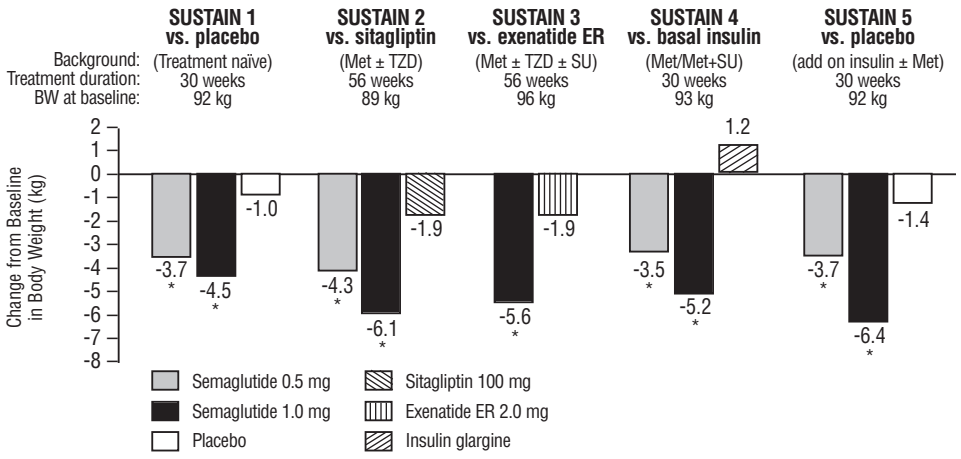
Incretin enhancing drugs, the glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) and the dipeptidyl peptidase-4 inhibitors (DPP-4i) have now been available for more than a decade. Their role in the management of Type 2 diabetes continues to evolve, with newer strategies and compounds continuing to be studied.

Semaglutide, an investigational, once-weekly GLP-1 RA, has been compared to multiple therapies in the SUSTAIN 1-5 clinical trials of patients with Type 2 diabetes. Lingvay and international colleagues reported the impact of this subcutaneously injected drug on body weight from these trials (abstract 243-OR) in comparison with placebo (SUSTAIN 1, treatment naïve); sitagliptin (SUSTAIN 2, on metformin ± thiazolidinedione [TZD]); extended-release exenatide (SUSTAIN 3, on metformin ± TZD ± sulfonylurea); insulin glargine (SUSTAIN 4, insulin-naïve on metformin/metformin ± sulfonylurea); and, placebo (SUSTAIN 5, on basal insulin ± metformin). Pre-specified analyses included change in body weight from baseline, percentage of patients achieving ≥5% and ≥10% reduction of body weight from baseline, as well as change in BMI and waist circumference. Statistically significant reductions in all parameters were achieved favoring semaglutide regardless of comparator (Figure 6), with the greatest impact observed in the 1 mg (vs. 0.5 mg) dosage of semaglutide.

In a related poster (abstract 1080-P), Ahmann and international researchers also utilized the dataset from the SUSTAIN 1-5 trials to examine the impact of semaglutide on glycemic control in Type 2 diabetes versus each of the comparators previously described. The primary endpoints for this analysis were change in HbA1c, fasting plasma glucose, and proportion of patients who achieved HbA1c targets. Similar to the results favoring semaglutide with body weight analysis, patients in the GLP-1 RA arms experienced greater HbA1c reduction (1.2-1.8% vs. 0.02-0.09%, p<0.0001) as well as a higher percentage of patients that achieved target HbA1c <7% and ≤6.5% (both p<0.0001). With the exception of semaglutide 0.5 mg versus insulin glargine (SUSTAIN 4), all semaglutide groups demonstrated statistically significant reductions in fasting plasma glucose versus comparators (-29.1 to -51.2 versus -8.5 to -38.2 mg/dL, p<0.0002).

We would remind our readers that this investigational GLP-1 RA was shown in the SUSTAIN-6 trial to be associated with a 26% relative risk reduction in CV events. The main concern from that trial was an increase in retinopathy in the active therapy group. Please refer to page 1, edition 1 for a further discussion of this new concern.

Figure 6. Weight Loss Observed with Semaglutide versus Comparators in the SUSTAIN 1-5 Trials



* p<0.001 vs. comparator. SUSTAIN 4: insulin glargine starting dose 10 IU once daily uptitrated to SMPG target of 72-99 mg/dL. SUSTAIN 5: All subjects were receiving stable treatment with basal insulin (minimum of 0.25 IU/kg/day and/or 20 IU/day of insulin glargine, insulin determir, insulin degludec and/or NPH insulin) ± metformin.
BW=body weight; exenatide ER=exenatide extended release; Met=metformin; SMPG=self-measured plasma glucose; SU=sulfonylurea; TZD=thiazolidinedione

Researchers from the US and Canada, Pantalone *et al.* evaluated the impact of dulaglutide when combined with insulin in patients with Type 2 diabetes, categorized by age (<65 and ≥65), diabetes duration (<10 and ≥10 years), and baseline HbA1c (≤9% and >9%) in a post-hoc analysis of the AWARD-4 and -9 trials (abstract 1089-P). AWARD-4 compared dulaglutide 1.5 mg with prandial lispro vs. glargine and prandial lispro. AWARD-9 compared dulaglutide with placebo, each added to insulin glargine. At 6 months in a pooled analysis of the two trials, dulaglutide significantly reduced HbA1c across all subgroups (p<0.001). As with most trials, the greatest reductions were seen in patients with baseline HbA1c values >9%. Weight loss was observed in all subgroups in both trials with the exception of three: diabetes duration <10 years (AWARD-4) and HbA1c >9% (both trials). Rates of severe and symptomatic hypoglycemia were comparable among all subgroups. From this analysis, the investigators concluded that dulaglutide is efficacious as combination therapy with prandial or basal insulin and is not impacted by age, diabetes duration, or baseline HbA1c. These data are consistent with those from other members of this class.

Another area of investigation with the GLP-1 RAs relates to their role in treatment intensification after basal insulin, specifically: What are the barriers to intensification and subsequent outcomes related to the treatment modality chosen? US colleagues, Kallenbach, *et al.*, examined data from the Practice Fusion Database (>25 million patients representing 6.7% of all US ambulatory care). The goal was to determine change in HbA1c from baseline and hypoglycemia rate as a function of intensification strategy (either adding a rapid-acting insulin analogue versus a GLP-1 RA versus another injectable [i.e., amylin mimetic, short-acting—i.e. human regular, or premixed insulin]) versus no intensification. Data from January 2011 through December 2015 identified 14,653 patients with poorly controlled (HbA1c >7.0%) Type 2 diabetes one to six months following initiation of basal insulin (identified as the index date). Of these, 2,121 patients had their basal insulin regimen intensified with one of the aforementioned treatment strategies within 6 months after the index date.

A predictor of intensification with a rapid-acting insulin or GLP-1 RA was associated with having an endocrinologist as the prescribing physician. Patients with a higher BMI or lower age were significantly associated with GLP-1 RA intensification. All intensification strategies monitored resulted in a greater decrease in HbA1c versus no intensification. Change in HbA1c, least squares mean (95% CI), were actually relatively modest across categories: rapid-acting insulin -0.276 (-0.421, -0.131); GLP-1 RA -0.311 (-0.535, -0.087); other injectable -0.22 (-0.459, 0.02); and no intensification -0.139 (-0.251,

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-0.028). One apparent advantage to intensification with a GLP-1 RA was that rates of hypoglycemia did not increase, but did so with all other strategies. From these data, the investigators suggested that any treatment intensification improves glycemia, but that use of a GLP-1 RA achieves the greatest HbA1c reduction and lowest hypoglycemia rate. We would, however, point out the relatively disappointing improvement in HbA1c across the strategies in this observational study.

Pooled populations from the FREEDOM-1 and -2 trials were used to identify treatment modalities that might delay the need for intensification or advancement of diabetes therapy. Henry and US collaborators evaluated 814 patients with uncontrolled (mean baseline HbA1c 8.6%) Type 2 diabetes receiving oral hypoglycemics (abstract 1078-P). The FREEDOM trials investigated ITCA 650 (n=414), an osmotic mini-pump system, placed subdermally, designed to deliver continuous subcutaneous release of exenatide, versus the DPP-4i, sitagliptin (n=257) or placebo (n=143). Per protocol, advancement of therapy was required after week 26 if HbA1c remained >8.0%. The need for advancement of therapy was far lower in the treatment group assigned to ITCA 650 when compared to the other treatment modalities. All groups required intensification at week 26, but 88% of ITCA 650 patients remained on their assigned therapy at week 39 (versus 74% on sitagliptin and 61% on placebo). The other treatment groups, sitagliptin and placebo, also demonstrated a progressive need for therapy advancement after week 26.

Two investigations assessed the utility of the fixed-dose basal insulin/GLP-1 combination (glargine/lixisenatide or "LixiLan"). This along with iDegLira, a new formulation of the basal insulin degludec and the GLP-1RA liraglutide, represent initial forays into a novel concept in Type 2 diabetes therapy—the use of injectables that contain fixed ratios of an insulin and an incretin drug. Frias and international colleagues assessed the time to glycemic control in those treated with glargine/lixisenatide versus insulin glargine alone in patients with uncontrolled Type 2 diabetes receiving oral hypoglycemics or basal insulin (abstract 1084-P). Data from the previously conducted LixiLan-O and LixiLan-L trials were analyzed via the Kaplan-Meier method to determine time to control as defined by days to first achievement of HbA1c <7% or fasting plasma glucose ≤130 mg/dl. Data from the LixiLan-O trial demonstrated that combination therapy with glargine/lixisenatide (n=469) achieved target HbA1c values in half the time versus glargine alone (n=467): 85.0 days versus 166.0 days (HR=1.5, p<0.0001) in 50% of patients. In the LixiLan-L study, the median time was 153.0 days for combination therapy, but target HbA1c was never achieved in the glargine group (HR=2.0; p<0.0001). With respect to fasting plasma glucose lowering, results were comparable between groups in both studies, however. This is likely explained by the short activity profile of lixisenatide—not long enough to control fasting glucose the next day. The investigators suggested use of the combination therapy results in earlier time to achieve targets and in a greater number of patients when compared with glargine alone.

Niemoeller and European and American colleagues assessed the magnitude of HbA1c lowering with the glargine/lixisenatide combination versus basal insulin alone (abstract 1079-P). Also utilizing data from the LixiLan-L study, the researchers examined differences in efficacy based on pre-study levels of glycemic control: HbA1c <8%, between 8% and <9.0%, and >9%. As anticipated, either regimen (glargine/lixisenatide or glargine) reduced HbA1c at the 30-week mark in each category with the greatest impact observed in patients with baseline values > 9%. In all categories, reductions in HbA1c were significantly greater with the glargine/lixisenatide combination (p<0.0001 for all when compared with glargine).

Although the GLP-1 RAs are not FDA-approved for Type 1 patients, research continues in this area. Dejgaard, *et al.*, Denmark reported the results of the Lira Pump trial (abstract 71-OR), which examined the efficacy and safety of liraglutide 1.8 mg when added to overweight patients (BMI >25 kg/m^2) with poorly controlled Type 1 diabetes (HbA1c >7.5%) receiving insulin pump therapy. Patients (n=44) were randomized to liraglutide or placebo for 26 weeks in addition to insulin pump treatment. Baseline characteristics were comparable between groups with respect to HbA1c, diabetes duration, body weight, and daily insulin dose. Change in HbA1c and body weight favored the liraglutide group (p<0.001), but there were no differences with respect to daily insulin dose, time spent in hypoglycemia (<70 mg/dL), heart rate, or blood pressure. One severe hypoglycemia event was reported. From these data, the researchers concluded that addition of liraglutide improves HbA1c and body weight in patients on insulin pump therapy without benefits on insulin requirements or hypoglycemia. These data, along with previously published work on this class, make us somewhat less enthusiastic for this approach in Type 1 diabetes.

Other incretin therapy topics covered this week include highly preliminary data with a novel oral form of semaglutide (abstracts 1191-P and 1192-P); the potential use of sitagliptin, a DDP-4i, in patients with Type 2 diabetes following bariatric surgery (it did not work) (abstract 134-OR); and the use of DPP-4i in the hospital setting (it did work—see tomorrow's edition.)

Table 2. Liraglutide versus Placebo Added to Insulin Pump Therapy in Patients with Type 1 Diabetes

	Liraglutide, n=22 (95% CI)	*Placebo, n=22 (95% CI)*	*Difference (95% CI)*	*p-value*
Change in HbA1c (%)	-0.4 (-0.7, -0.2)	0.2 (0.0, 0.5)	-0.6 (-1.0, -0.3)	<0.001
Change in body weight (kg)	-6.4 (-7.9, -4.9)	-0.7 (-2.1, 0.8)	-5.7 (-7.9, -3.6)	<0.001
Change in daily insulin dose (IU/day)	0.5 (-2.1, 3.1)	2.5 (0.1, 5.0)	-2.0 (-5.6, 1.6)	0.270
Change in time spent in hypoglycemia (%)*	0.3 (-2.6, 3.2)	2.0 (-0.7, 4.7)	-1.7 (-5.6, 2.2)	0.397
Change in systolic blood pressure (mm Hg)	-3.7 (-9.2, 1.8)	-3.1 (-8.3, 2.1)	-0.6 (-8.2, 7.0)	0.880
Change in diastolic blood pressure (mm Hg)	-0.1 (-2.7, 2.5)	0.1 (-2.4, 2.5)	-0.2 (-3.8, 3.4)	0.921
Change in heart rate (beats/min)	5.4 (1.1, 9.7)	0.3 (-3.8, 4.3)	5.1 (-0.7, 11.0)	0.086

*Glucose <70 mg/dl assessed by 1 week of blinded continuous glucose monitoring at baseline, 13 weeks, and 26 weeks.

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