

Exclusive Coverage of the

## AMERICAN DIABETES ASSOCIATION 77TH SCIENTIFIC SESSIONS

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### Overview of the CANVAS Program

Investigators of the Canagliflozin Cardiovascular Assessment Study (CANVAS) program presented an integrated analysis of 2 large cardiovascular (CV) outcome trials of canagliflozin at the American Diabetes Association 77th Scientific Sessions in San Diego, California, held June 9-13, 2017. The CANVAS Program, which includes both the CANVAS and CANVAS-R trials, enrolled more than 10,000 patients from 30 countries. Canagliflozin demonstrated superiority compared with placebo in improving CV event outcomes and renoprotective activity in patients with type 2 diabetes (T2D).<sup>1</sup>

Canagliflozin is an oral agent indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D at dosages of 100 mg and 300 mg.<sup>1,2</sup> Canagliflozin is an active inhibitor of sodium-glucose co-transporter-2 (SGLT-2), which mediates glucose reabsorption in the kidney by actively transporting glucose; approximately 90% of glucose filtered by the kidney is reabsorbed by SGLT-2, which is present in the S1 and

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### Real-World Outcomes With SGLT-2 Inhibitors: Analysis of Efficacy in Clinical Use

Canagliflozin is one of the subtype sodium-glucose co-transporter-2 (SGLT-2) inhibitors belonging to the gliflozin class of antidiabetic agents. The gliflozin class includes canagliflozin, empagliflozin, dapagliflozin, and an investigational agent, ertugliflozin. The SGLT-2 inhibitor class agents have demonstrated efficacy and safety in the landmark EMPA-REG Outcomes trial and in the breakthrough results of the CANVAS Program, presented at the American Diabetes Association 77th Scientific Sessions. In these trials, patients with type 2 diabetes (T2D) and established cardiovascular disease (CVD) have achieved reductions in the risk of hospitalization for heart failure (HF), and in the 3-point composite outcome of major adverse cardiovascular events. The cardiovascular safety and efficacy of dapagliflozin are currently being investigated in 17,276 patients with T2D who are at high risk for cardiovascular events, in the placebo-controlled, phase 3b/4 DECLARE-TIMI 58 trial.<sup>1</sup>

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## Overview of the CANVAS Program (Continued from page 1)

S2 segments of the proximal convoluted tubule.<sup>1,3</sup> Renal glucose reabsorption is elevated in patients with T2D, as highly filtered glucose exceeds the reabsorption threshold. This leads to glucose excreted in the urine.<sup>1</sup> Inhibiting SGLT-2 suppresses glucose reabsorption and increases urinary glucose excretion, which facilitates reduced glucose levels in circulation. This inhibition may facilitate beneficial CV impacts, and may lead to lower blood glucose, lower blood pressure through osmotic diuresis, and an increase in urinary caloric loss represented as reductions in body weight. SGLT-2 inhibition has a potential renoprotective effect through reduction of albuminuria due to alterations in the tubuloglomerular feedback system.<sup>1</sup>

The CANVAS trial was a double-blind, placebo-controlled study investigating the efficacy and safety of canagliflozin on the risk of cardiovascular disease (CVD) in patients with inadequately controlled T2D and increased CVD risk. It enrolled 4330 patients with T2D randomized (1:1:1) to receive 100 mg or 300 mg of canagliflozin or placebo.<sup>1,2</sup>

The CANVAS-R study was a second large, prospective, randomized, double-blind, placebo-controlled clinical trial of patients with T2D with a history or a high risk of CV events.<sup>2</sup> The separate primary objective of CANVAS-R was attenuation of kidney disease progression, as evidenced by fewer incidences of albuminuria progression.<sup>2</sup> CANVAS-R was initiated in 2012 after marketing was authorized in the United States following the achievement of CV safety outcomes in the CANVAS trial. Data from the ongoing CANVAS trial were combined with CANVAS-R trial data to address the specified postmarketing safety requirements.<sup>2</sup> The CANVAS-R trial randomized 5812 patients to once-daily placebo or canagliflozin 100 mg, with optional up-titration to 300 mg.<sup>2</sup>

In an analytic approach of the CANVAS Program, the trials were combined to evaluate the entire intention to treat

population (N = 10,142).<sup>1</sup> Patients with T2D were defined as having inadequate glyce-mic control if glycated hemoglobin (A1C) was between 7.0% and 10.5%. The mean baseline A1C was 8.2% in both placebo and canagliflozin arms.<sup>2</sup> Patients 30 years or older with T2D were enrolled based on criteria for established CVD with a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular, or peripheral).<sup>2</sup> Alternatively, patients at least 50 years or older were enrolled if they had 2 or more CV risk factors, including a duration of T2D of at least 10 years, systolic blood pressure >140 mm Hg while on 1 or more antihypertensive agents, were currently smokers, had microalbuminuria or macroalbuminuria, or had high-density lipoprotein cholesterol <1 mmol/L.<sup>1</sup>

Of the total patient population in the CANVAS Program, baseline characteristics were well balanced between the canagliflozin and placebo arms.<sup>2</sup> Patients enrolled could be naïve to antihyperglycemic treatment or treated with monotherapy or combination therapy for glycemic control; metformin treatment was used in the majority of the population (77%), with insulin (50%) and sulfonylureas (43%) also noted. Treatment with newer oral glucose-lowering agents was less common: 4% of the study population received glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and 12% were treated with dipeptidyl peptidase 4 inhibitors. Standard-of-care treatment for the management of comorbidities in patients with diabetes was followed according to local guidelines: renin angiotensin aldosterone system inhibitors (80%), statins (75%), antithrombotic agents (73%), beta-blockers (53%), and diuretics (44%).<sup>1,2</sup>

To demonstrate long-term CV protection, adverse events were assessed at a follow-up at a median of 3.6 years (188.2 weeks). At follow-up, it is noteworthy that 71% of patients in the canagliflozin arm and 70% in the placebo arm were still on study treatment.<sup>1</sup> The primary end point of the CANVAS Program was to

demonstrate noninferiority of canagliflozin treatment compared with placebo and to demonstrate a reduction of the most common serious vascular outcomes in patients with T2D. Hypothesis testing was based on prespecified analysis criteria of statistical significance, noninferiority, and superiority to placebo on the outcomes of all-cause mortality and the composite CV outcome of vascular death, nonfatal myocardial infarction (MI), and nonfatal stroke.<sup>1</sup>

### Superior Cardiovascular Safety of Canagliflozin

Bruce Neal, MB ChB, PhD, a senior director of the George Institute for Global Health in Australia, presented the CV outcomes from the CANVAS trial, which found canagliflozin treatment reduced the risk of primary CV outcomes by 14%. Canagliflozin was found to be noninferior to placebo ( $P < .0001$ ) in the reduction of the event rate of death from CV causes, nonfatal MI, or nonfatal stroke (TABLE 1).<sup>1,4</sup> The canagliflozin arm achieved significant reductions in the total event rate of major adverse cardiac events (MACE) outcomes with a total of 26.9 events per 1000 patient-years compared with 31.5 events in the placebo arm (HR, 0.86; 95% CI, 0.75-0.97;  $P < .0001$ ).<sup>4</sup> Canagliflozin also demonstrated superiority to placebo in the reduction of primary MACE outcomes ( $P = .0158$ ).<sup>1</sup> Overall, this reduction in CV outcomes translates to > 5 years of treatment in 1000 patients and shows that canagliflozin treatment will prevent MACE incidence in 23 more patients compared with placebo.<sup>1,4</sup>

Compared with placebo treatment, canagliflozin reduced the risk of individual primary CV outcomes, including CV death (HR, 0.87; 95% CI, 0.72-1.06), nonfatal MI (HR, 0.85; 95% CI, 0.69-1.05), and nonfatal stroke (HR, 0.90; 95% CI, 0.71-1.15). Canagliflozin treatment was favored compared with placebo in the key secondary end points of hospitalization for heart failure (HF) and the composite of CV mortality and hospitalization for HF. Canagliflozin reduced the risk of HF hospitalization by 33% compared with placebo (HR, 0.67; 95% CI, 0.52-0.87). This translates to a reduction in the incidence of HF hospitalizations in 16 fewer patients treated with canagliflozin compared with placebo.<sup>4</sup>

End points of the CANVAS trial also assessed key biomarkers measuring microvascular and macrovascular risk outcomes, including blood pressure, A1C, and body weight, which is a risk factor for many comorbidities with CVD and diabetes.<sup>1</sup> Canagliflozin reduced mean A1C over the 6 years of randomization by 0.58% more than placebo, with a drastic glucose-lowering effect in the beginning of randomization with steady lowered A1C compared with placebo.<sup>1</sup>

**Table 1.** CANVAS Program Efficacy Outcomes<sup>1,4</sup>

Efficacy Outcomes	Canagliflozin N = 5795	Placebo N = 4347	Hazard Ratio (95% CI)	P
	Event rate per 1000 patient-years			
Primary MACE Outcomes <sup>a</sup>	26.9	31.5	0.86 [0.75-0.97]	< .0001 for noninferiority = .0158 for superiority
Individual CV Outcomes				
Death from CV	11.6	12.8	0.87 [0.72-1.06]	--
All cause mortality	17.3	19.5	0.87 [0.74-1.01]	--
Nonfatal MI	9.7	11.6	0.85 [0.67-1.05]	--
Nonfatal stroke	7.1	8.4	0.90 [0.71-1.15]	--
Hospitalization for HF	5.5	8.7	0.67 [0.52-0.87]	--
Composite renal outcomes <sup>b</sup>	5.5	9	0.60 [0.47-0.77]	--

CV indicates cardiovascular disease; HF, heart failure; MACE, major cardiac events; MI, myocardial infarction.

<sup>a</sup>CV death, nonfatal myocardial infarction, or nonfatal stroke.

<sup>b</sup>Composite endpoint of 40% reduction in eGFR, end-stage renal disease, or renal death.

Adapted from Neal B, Perkovic V, Mahaffey KW, et al. *N Engl J Med*. 2017 [Epub ahead of print].

Canagliflozin treatment significantly reduced mean systolic blood pressure compared with placebo, with a mean reduction of 3.39 mm Hg from baseline over the study, and a greater reduction, compared with placebo, by 1.60 kg (95% CI, -1.70 to -1.51) in the mean difference in body weight associated with canagliflozin treatment.<sup>4</sup>

### Renal Outcomes

The renoprotective effects of canagliflozin were presented by Dick De Zeeuw, MD, PhD, chair and professor of clinical pharmacy at the University of Groningen in the Netherlands. Canagliflozin treatment significantly reduced the progression of albuminuria; fewer patients in the canagliflozin arm experienced progression, defined as a change in albuminuria class, compared with the placebo arm. Progression events occurred in patients treated with canagliflozin at a rate of 89.4 per 1000 patient-years compared with 128.7 events per 1000 patient-years (HR, 0.73; 95% CI, 0.67-0.79) in those treated with placebo. This renoprotective effect was greater in the population of the CANVAS-R trial, in which there was a larger patient population with chronic kidney disease (HR, 0.64; 95% CI, 0.57-0.73) than there was in CANVAS (HR, 0.80; 95% CI, 0.72-0.90) ( $P = .02$  for homogeneity). Regression of albuminuria also occurred more frequently among those assigned to canagliflozin than among those assigned to placebo (293.4 vs 187.5 participants with regression per 1000 patient-years; HR, 1.70; 95% CI, 1.51-1.91).<sup>1,4</sup>

Canagliflozin significantly lowered the risk of the composite renal decline, defined by sustained 40% reduction in eGFR and the requirement of renal-replacement therapy, or death from renal causes (Table 1<sup>4</sup>).<sup>1</sup> Patients treated with canagliflozin were 40% less likely to suffer serious kidney decline; 5.5 patients in the canagliflozin arm experienced renal outcomes per 1000

**Table 2.** CANVAS Program Safety Outcomes<sup>1,4</sup>

Safety Outcomes	Canagliflozin N = 5795	Placebo N = 4347	Hazard Ratio (95% CI)	P Value
All serious adverse events	104	120	0.93 (0.87-1.00)	.04
Adverse events of interest across program				
Amputation	6.3	3.4	1.97 (1.41-2.75)	<.001
Venous thromboembolism	1.7	1.7	0.96 (0.54-1.71)	
Infection of male genitalia <sup>a</sup>	34.9	10.8	3.76 (2.91-4.86)	<.001
Photosensitivity	1	0.3	2.71 (0.92-8.03)	.07
Adjudicated diabetic ketoacidosis	0.6 <sup>b</sup>	0.3	2.33 (0.76-7.17)	.14
Adjudicated acute pancreatitis	0.5	0.4	1.34 (0.40-4.41)	.63
Adjudicated fractures	15	12	1.26 (1.04-1.52)	.005

<sup>a</sup>Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.

<sup>b</sup>5 patients from the canagliflozin arm reporting diabetic ketoacidosis identified as having autoimmune diabetes.

Adapted from Neal B, Perkovic V, Mahaffey KW, et al. *N Engl J Med*. 2017 [Epub ahead of print].

**Table 3.** Summary of Canagliflozin Treatment Outcomes<sup>1,4</sup>

CANVAS Outcomes	Canagliflozin vs placebo treatment over 5 years, affected per 1000 patients
Composite of CV death, nonfatal myocardial infarction, or nonfatal stroke	23 fewer patients
Hospitalization for heart failure	16 fewer patients
Composite of 40% reduction in eGFR, end-stage renal disease, or renal death	17 fewer patients
Amputation	15 more patients <ul style="list-style-type: none"> <li>• 5 above ankle</li> <li>• 10 toes and metatarsals</li> </ul>

CV indicates cardiovascular; eGFR, estimated glomerular filtration rate.

Adapted from Neal B, Perkovic V, Mahaffey KW, et al. *N Engl J Med*. 2017 [Epub ahead of print].

patient-years compared with 9 patients in the placebo arm (HR, 0.60; 95% CI, 0.47-0.77). Of the total serious kidney decline events, there were 239 events of 40% estimated glomerular filtration rate reduction and 21 events of end-stage renal disease or renal death.<sup>1,4</sup>

### Safety Outcomes

The effects on safety outcomes were presented by Vlado Perkovic, MBBS, PhD, executive director of The George Institute, Australia (TABLE 2<sup>1,4</sup>). In the CANVAS trial, risks of both low-trauma fracture and all fracture were higher than in the CANVAS-R trial; canagliflozin-treated patients experienced a higher rate of all fractures and low-trauma fracture events than placebo-treated patients. Previously reported risks of adverse events with canagliflozin versus placebo were also observed in the CANVAS trial in events per 1000 patient years, such as infections of male genitalia (34.9 vs 10.8), female mycotic genital infection (68.8 vs 17.5), volume depletion (26 vs 18.5), and diuresis (34.5 vs 13.3). Despite low incidence of diabetic ketoacidosis events overall, they were more frequent in the canagliflozin treatment group, with 0.6 patients experiencing an event for every 1000 patients treated with canagliflozin, versus 0.3 patients with placebo treatment (HR, 2.33; 95% CI, 0.76-7.17).<sup>1,4</sup>

Canagliflozin treatment was associated with a 2-fold increase in risk for amputation (HR, 1.97; 95% CI, 1.41-2.75;  $P < .001$ ). The CANVAS-R trial showed that over a year's time, the risks of amputation for patients in the trial were equivalent to 7.5 patients of every 1000 patients treated with canagliflozin and 4.2 patients of every 1000 patients treated with placebo. The CANVAS trial showed the risks of amputation for patients in the trial were equivalent to 6.3 patients of every 1000 patients treated with canagliflozin and 3.4 patients of every 1000 patients treated with placebo. This translates to 15 more patients with amputations of 1000 per patient-years over 5 years, compared with placebo.<sup>1,4</sup>

Investigators stratified the study population to identify potential risk factors associated with amputation risk. History of amputation was largely associated with amputation in both treatment arms (HR, 20.9; 95% CI, 14.2-30.8). Peripheral vascular disease at baseline was a predisposing factor related to amputations in both treatment arms (HR, 3.1; 95% CI, 2.2-4.5). Canagliflozin treatment (HR, 1.8; 95% CI 1.5-2.5) and uncontrolled diabetes with an A1C >8% (HR, 1.9; 95% CI, 1.4-2.6) posed similar risks

for amputation events.<sup>1</sup> Neal stated, "We don't know why there was an increased risk of amputation, and further work is needed in this area. But for now, we urge caution in prescribing this drug to people at increased risk of suffering amputation." The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREEDENCE) trial will offer additional evidence supporting clinical impact of canagliflozin treatment on kidney outcomes.<sup>1</sup>

Canagliflozin is the second SGLT-2 inhibitor to demonstrate superiority in the reduction of CV events compared with placebo treatment. Overall, the most clinically relevant risk of canagliflozin treatment is an increased risk of amputations, especially in the patient population who are predisposed to amputation risk.

The most clinically relevant benefits of canagliflozin are magnified in the population at highest risk of CV events; those with a history of CV disease have the greatest benefit with canagliflozin treatment in reduction in the risk of CV death, nonfatal myocardial infarction or nonfatal stroke, all cause mortality, and CV death. Canagliflozin also offers benefits in reduction of heart failure-related hospitalizations, offers renal protection, has glucose-lowering efficacy, and

is associated with improvements in body weight and blood pressure (TABLE 3).<sup>1,4</sup> ●

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### Real-World Outcomes With SGLT-2 Inhibitors (Continued from page 1)

#### Cardiovascular Safety of the SGLT-2 Inhibitor Class: CVD-REAL Trial

Results of the CVD-REAL trial were presented at the American Diabetes Association 77th Scientific Sessions by Matthew A. Cavender, MD, MPH, FACC, assistant professor of medicine in the Division of Cardiology at the University of North Carolina School of Medicine in Chapel Hill. The CVD-REAL trial demonstrated the class effect benefit of SGLT-2 inhibitors compared with other glucose-lowering oral agents (metformin, sulfonylureas, dipeptyl peptidase 4 [DPP-4] inhibitors, thiazolidinediones, glucagon-like peptide 1 receptor agonists [GLP-1 RAs], insulin) to reduce cardiovascular events in patients with T2D, regardless of CVD history.<sup>2</sup>

In this large, multinational, real-world, evidence-based analysis of 306,156 patients with T2D, patients were identified using the following: blinded national registry data from Sweden, Norway, and Denmark; US registry and claims data collected from Truven Health MarketScan Claims and Encounters, linked Medicare Supplemental databases, and electronic health and death records; and Clinical Practice Research Datalink and The Health Improvement Network medical records from the United Kingdom. Patients with T2D who either had established CVD or absence of CVD were matched by baseline characteristics and stratified (1:1) into analysis cohorts based on initiation of glucose-lowering therapy or SGLT-2 inhibitors. Events were analyzed per 100 patient-years, where the cohort treated with SGLT-2 inhibitors totaled 100,947 patient years and the cohort treated with other glucose-lowering therapies totaled 89,208 patient years.<sup>2</sup>

The event rates of the composite of HF and death, as well as individual events of all-cause death and HF, were generally lower in patients without established CVD. The SGLT-2 inhibitor treatment arm had significantly fewer absolute rates of all measured cardiovascular events, compared with the arm using other glucose-lowering therapies ( $P < .001$ ). All cardiovascular event rates were significantly ( $P < .001$ ) lower in patients with and without established CVD in whom treatment with SGLT-2 inhibitors was initiated compared with patients in whom other glucose-lowering therapies were initiated. In the composite

endpoint, patients with established CVD had an absolute rate of 3.6 events per 100 patient-years with SGLT-2 inhibitors compared with 6.8 per 100 patient-years with other glucose-lowering agents.<sup>2</sup>

Patients new to SGLT-2 inhibitors, compared with those receiving other glucose-lowering therapies, experienced reduction in the rates of all-cause mortality by 45% ( $P < .001$ ) and hospitalization for HF by 31% ( $P < .001$ ). Initiation of therapy with an SGLT-2 inhibitor reduced the risk for composite events of HF-associated hospitalizations and mortality; risk reductions were similar in patients with established CVD (HR, 0.59; 95% CI, 0.52-0.67) and without CVD (HR, 0.52; 95% CI, 0.44-0.61). In the primary outcome of composite all-cause mortality or hospitalization for HF of 215,622 patients, events were lower in the patient group without prior CVD (899 events) compared with those with prior CVD (1084 events); the risk reduction with an SGLT-2 inhibitor was similar in both cohorts, with the SGLT-2 inhibitor providing a more significant benefit than other glucose-lowering therapy ( $P < .001$ ). Of the total US population ( $N = 143,264$ ), 424 composite cardiovascular events occurred, and SGLT-2 was associated with a reduction in the rate of events (HR, 0.44; 95% CI, 0.36-0.54;  $P < .001$ ) for the comparison (TABLE 1).<sup>2</sup>

Notably, in this large multinational analysis, the majority of the enrolled patient population with T2D did not have established CVD. Consistency of findings across countries, where different SGLT-2 inhibitors were used, shows that the benefit of this class of agents is not only generalizable to a large patient population, but for all patients with T2D, regardless of CVD presence on initiation of therapy. Patients with and without established CVD are at lower risk of both death and HF in the first 8 months after initiation of SGLT-2 inhibitors compared with other glucose-lowering therapies.

In a separate analysis of the CVD-REAL trial using the Nordic registry for data of patients with T2D ( $N = 34,328$ ), initiation of dapagliflozin was associated with reduced risk of hospitalizations for kidney disease, hospitalization for HF, and all-cause mortality, compared with initiation of DPP-4 inhibitors.<sup>3</sup>

Two additional significant investigations on the real-world utilization, efficacy, and costs associated with the SGLT-2 inhibitor canagliflozin, compared with other antidiabetic class agents, were presented at the American Diabetes Association's 77th Scientific Sessions.

**Table 1. CVD-REAL Trial SGLT-2 Inhibitor Cardiovascular Event Reduction<sup>2</sup>**

Composite endpoint (HF or all-cause mortality)	Number of patients	Number of events	Hazard ratio (95% CI)
Total population	215,622	1983	0.54 (0.48-0.60)
With established CVD	30,153	1084	0.59 (0.52-0.67)
Without established CVD	185,469	899	0.52 (0.44-0.61)
Total United States patient population	143,264	424	0.44 (0.36-0.54)

CVD indicates cardiovascular disease; SGLT-2, sodium-glucose co-transporter-2.

Adapted from Cavender MA, Norhammar A, Birkeland KI, et al; the CVD-REAL Investigators and Study Group. Presented at: 77th Scientific Sessions of the American Diabetes Association; June 9-13, 2017; San Diego, CA. Abstract 377-OR.

### Cardiovascular Safety of Canagliflozin Versus Nongliflozin Class Agents

Elisabetta Paterno, MD, DrPH, assistant professor of medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology & Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, presented results from a retrospective analysis investigating the cardiovascular safety of canagliflozin administered in the routine clinical care setting for the treatment of patients with T2D. The study was designed to compare the cardiovascular risk of the routine use of canagliflozin, representing agents of the SGLT-2 inhibitor class, with the cardiovascular risk of use of other antidiabetic agents used in routine care not within the gliflozin class, including DPP-4 inhibitors, GLP-1 RAs, and second-generation sulfonylureas.<sup>4</sup>

In this retrospective analysis, 224,999 adult patients with T2D were identified using more than 2 years of prescription claims data, April 2013-September 2015, from a large commercial US health insurance database. Investigators balanced the study population by newly filled prescriptions of antidiabetic agents into 3 pairwise (1:1) propensity score-matched treatment cohorts for analysis of canagliflozin to comparators (DPP-4 inhibitors, second-generation sulfonylureas, GLP-1 RAs). Patients were stratified by baseline characteristics for subgroup analyses; the association of established CVD at baseline was analyzed in the evaluation of the composite cardiovascular outcome of MI or stroke events. Patients with HF at baseline were analyzed within the cohorts to determine the association with HF hospitalization among the oral treatments.<sup>4</sup>

Over a follow-up of 30 months after treatment initiation, the canagliflozin arm provided no significant differences in the risk of the primary composite endpoint (MI or stroke) compared with DPP-4 inhibitors (HR, 0.89; 95% CI, 0.68-1.17), GLP-1 RAs (HR, 1.03; 95% CI, 0.79-1.35), or sulfonylureas (HR, 0.86; 95% CI, 0.65-1.13). Patients with established CVD had a similar risk for the key secondary outcomes, including the composite cardiovascular endpoint, as adjudicated outcome of hospitalization for MI, stroke, unstable angina, or coronary

revascularization individual analyses of cardiovascular events of MI or stroke hospitalization, and HF hospitalization.<sup>4</sup>

Across all 3 study cohorts, patients treated with canagliflozin had a decreased risk of HF hospitalization. Treatment with canagliflozin demonstrated the greatest decreased risk of HF hospitalizations compared with the second-generation sulfonylureas: 7.3% event rate in the canagliflozin group compared with a 14.4% rate with sulfonylurea treatment (HR, 0.51; 95% CI, 0.38-0.67). The canagliflozin group experienced 91 events compared with 124 in the DPP-4 inhibitor treatment group (HR, 0.70; 95% CI, 0.54-0.92). Previously, the DPP-4 inhibitors (sitagliptin, alogliptin) had shown higher rates of HF hospitalizations in cardiovascular outcomes trials and GLP-1 agonists (eg, lixisenatide) had shown no reduction compared with placebo. In this analysis, there were decreased HF hospitalization events with canagliflozin compared with GLP-1 RA (HR, 0.61; 95% CI, 0.47-0.78); 94 hospitalization events occurred in the canagliflozin arm compared with 148 events in the GLP-1 RA treatment arm (TABLE 2).<sup>4</sup>

In the key secondary outcomes, canagliflozin treatment was also associated with a lower risk of the adjudicated HF expanded event outcomes, including events of HF hospitalizations and/or new use of loop diuretics across all 3 treatment cohorts, with the lowest risk compared with sulfonylurea treatment (HR, 0.47; 95% CI, 0.39-0.56).<sup>4</sup> Canagliflozin was more effective, versus all comparator agents, in the reduction of hospitalization for patients experiencing HF who had an increased risk based on HF history at baseline and in those patients without previous HF. Risk reduction was similar across all treatment comparisons and in both patient risk groups. However, compared with DPP-4 inhibitor treatment, canagliflozin reduced the risk of HF hospitalization in patients with a history of HF to a greater extent than in those without a history of HF (HR, 0.59; 95% CI, 0.42-0.82, vs HR, 0.79; 95% CI, 0.52-1.21, respectively).<sup>4</sup>

Canagliflozin's ability to reduce HF hospitalization events was demonstrated in the CANVAS Program, and this real-world analysis presented by Paterno demonstrated that canagliflozin was associated with lowered risk of HF hospitalization or HF-related events. In this study, canagliflozin consistently reduced hospitalization for HF compared with nongliflozin agents, indicating that clinical usage of canagliflozin in patients with T2D offers cardioprotective function by reducing the risk of HF hospitalization. Compared with other antidiabetic agents, including GLP-1 RAs, canagliflozin was associated with fewer HF hospitalizations.<sup>4</sup>

### Real-World Glycemic Control With Canagliflozin Versus GLP-1 RAs: Cost Efficacy

In a separate real-world head-to-head analysis of the cost-effectiveness of glycemic control medications for patients with T2D, initiation of canagliflozin was compared with GLP-1 RAs.<sup>5</sup>

**Table 2.** Canagliflozin Reduces Heart Failure Hospitalization Rates Compared With Other Glucose-Lowering Therapies in Clinical Use<sup>4</sup>

Subgroup analysis/ endpoints	PS matched (1:1) cohort, canagliflozin vs DPP-4i (N = 17,667)			S matched cohort (1:1), canagliflozin vs GLP-1 RA (N = 20,539)			PS matched cohort (1:1), canagliflozin vs sulfonylureas (N = 17,354)		
	Canagliflozin (IR <sup>a</sup> )	DPP-4i (IR <sup>a</sup> )	HR (95% CI)	Canagliflozin (IR <sup>a</sup> )	GLP-1 RA (IR <sup>a</sup> )	HR (95% CI)	Canagliflozin (IR <sup>a</sup> )	Sulfonylureas (IR <sup>a</sup> )	HR (95% CI)
HF hospitalization <sup>b</sup>	91 (8.9)	124 (12.8)	0.70 (0.54-0.92)	77 (7.3)	154 (14.4)	0.51 (0.38-0.67)	94 (7.5)	148 (12.4)	0.61 (0.47-0.78)
Patients with HF history	--	--	0.59 (0.42-0.82)	--	--	0.59 (0.41-0.86)	--	--	0.62 (0.44-0.89)
Patients without HF history	--	--	0.79 (0.52-1.51)	--	--	0.58 (0.37-0.90)	--	--	0.63 (0.42-0.94)

DPP-4i indicates dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; PS, propensity score.

<sup>a</sup>IR per 1000 person-years.

<sup>b</sup>In patients without use of loop diuretics at baseline/patients without heart failure diagnosis at baseline.

Adapted from Paterno E, Goffine AB, Schneeweiss S, Glynn R, Liu J, Kim S. Presented at: 77th Scientific Sessions of the American Diabetes Association; June 9-13, 2017; San Diego, CA. Abstract 1497-P.

Carol H. Wysham, MD, clinical professor of medicine at the University of Washington School of Medicine, and section head of The Rockwood Center for Diabetes and Endocrinology at Rockwood Clinic in Spokane, Washington, presented the results.

Patients with T2D who initiated treatment with canagliflozin (n = 5540) or a GLP-1 RA (n = 17,477) were identified using electronic medical records obtained from a US database, which contains claims data for more than 35 million patients from all payer types. The data were collected from primary care providers (40%) and specialists (60%) from Quintiles IMS Real-World Data Electronic Medical Records, between late March 2012 and late April 2016.<sup>5</sup>

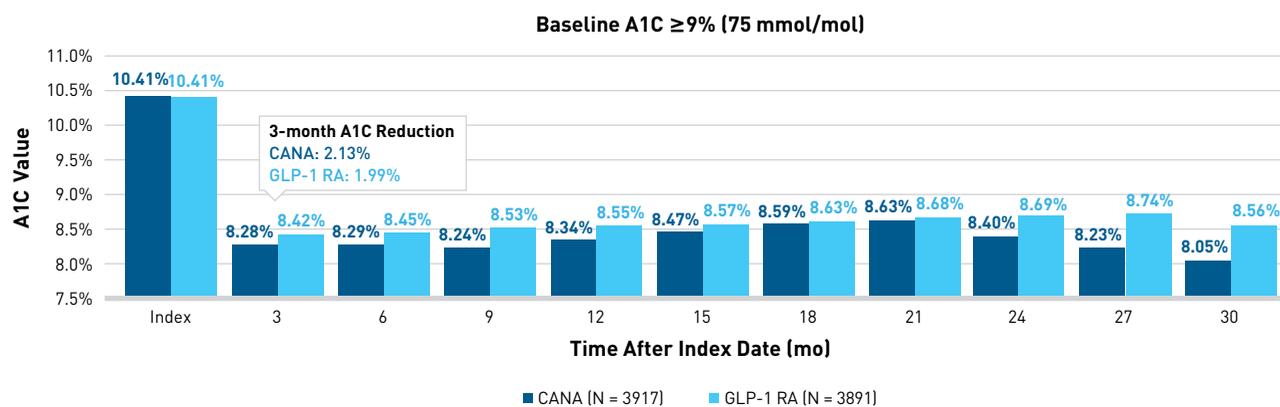
The primary study outcome identified glycemic control measured by glycated hemoglobin (A1C) change from 3 months post index date for up to 30 months. Patients were stratified by agent used (GLP-1 RA vs canagliflozin) and baseline A1C values. Following initiation with canagliflozin (300 mg dose), patients with uncontrolled diabetes at index (A1C ≥7%) experienced a 1.16% reduction in A1C 3 months following treatment. Initiation

of canagliflozin resulted in similar A1C values compared with GLP-1 RA treatment within 12 months post index; A1C values were lower with canagliflozin treatment from 6 to 18 months compared with treatment with a GLP-1 RA.<sup>5</sup>

Canagliflozin treatment consistently improved glycemic control over 30 months compared with GLP-1 RA use in patients with the highest degree of uncontrolled diabetes (A1C ≥9%) at index. In the 3 months following initiation with canagliflozin, these patients experienced A1C reductions of 2.11% compared with 1.99% with GLP-1 RA treatment (**FIGURE 1**).<sup>5</sup>

Based on wholesale acquisition price, the difference between per-patient per-day cost of canagliflozin (\$13.06) and GLP-1 RA class (\$22.17) lead to an average savings of \$9.11 with canagliflozin. Modeled treatment per-patient per-year costs were \$4767 for canagliflozin compared with \$8093 for GLP-1 RA therapy, for annual savings of \$3326 per patient with continuous use of canagliflozin. Additionally, patients who initiated treatment with canagliflozin achieved lower glucose levels over the course of 30 months (**FIGURE 2**).<sup>5</sup>

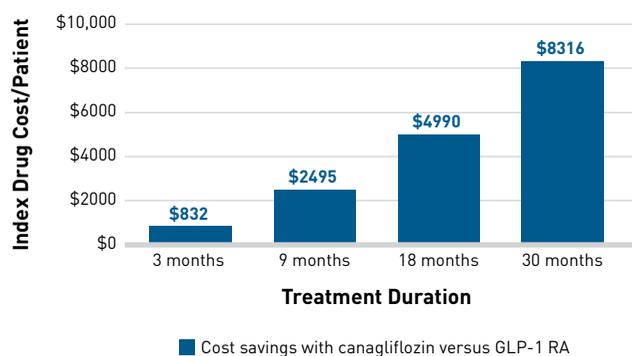
**Figure 1.** Canagliflozin-Mediated Glycemic Control in Patients with A1C ≥9%<sup>5</sup>



A1C indicates glycated hemoglobin; CANA, canagliflozin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; mo, month.

Adapted from Wysham CH, Pilon D, Ingham M, et al. Presented at: 77th Scientific Sessions of the American Diabetes Association; June 9-13, 2017; San Diego, CA. Abstract 1253-P.

**Figure 2.** Real-World Cost Efficacy of Initiation of Therapy With Canagliflozin Over 30 Months<sup>5</sup>



GLP-1 RA indicates glucagon-like peptide-1 receptor agonist.

Adapted from Wysham CH, Pilon D, Ingham M, et al. Presented at: 77th Scientific Sessions of the American Diabetes Association; June 9-13, 2017; San Diego, CA. Abstract 1253-P.

### Summary

These studies presented at the ADA's 77th Scientific Sessions demonstrated the real-world efficacy of SGLT-2 inhibitor class agents, in the reduction of risk of HF-associated hospitalizations and of mortality, compared with other glucose-lowering agents.

Specifically, canagliflozin was associated with a lower rate of HF hospitalizations compared with DPP-4 inhibitors, second-generation sulfonylureas, and GLP-1 RAs. This effect was observed in both high-risk and low-risk patient populations with T2D (based on HF history at baseline). In addition, canagliflozin was found to have lower real-world costs associated with treatment, compared with GLP-1 RAs. ●

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## Integrating Cardiovascular Trial Outcomes of Antihyperglycemic Agents into Diabetes Management Guidelines

Given the close association of comorbid heart disease in patients with type 2 diabetes (T2D), the 77th Scientific Sessions of the American Diabetes Association (ADA), have grown to involve experts from the fields of endocrinology and cardiology. This enhances the integration of more comprehensive, multidisciplinary treatment strategies into the management and care of patients living with these comorbidities. Steven Nissen, MD, chairman of the Department of Cardiovascular Medicine at Cleveland Clinic, noted an important societal effect of the cardiovascular outcome trials (CVOTs) for new agents in the treatment of diabetes: the gathering of experts from multiple disciplines to determine how to treat these patients.<sup>1</sup>

Following the 2008 FDA guidance indicating the need to ascertain the cardiovascular (CV) safety of all new antihyperglycemic agents, 30 trials are now ongoing. The insight and purpose behind this FDA decision was to ensure that these agents could remain on the market and be continuously available for the population of patients with diabetes at highest risk for CV events. The previous 50 years had passed with no trials to evaluate CV outcomes in this patient population. Nissen noted that we are in a “new era of research with outcome trials. The number of patients in outcome trials is enormous, and we are reaping the harvest from seeds

sown in 2008.” With the renaissance of CVOTs, clinicians now have evidence-based conclusions to guide the prevention of morbidity and mortality in patients with elevated risk.<sup>1</sup>

These trials have provided not only additional safety data and information, but unexpected insights into class agents in clinical use. Across the initial trials, there was diversity among agent classes: some agents were found to provide benefits in glycemic control, or to reduce morbidity and mortality, while others increased the risk of CV events. Prior to these trials, there was an absence of safety information on these agents' macrovascular effects—most emphasis was focused on their glucose-lowering abilities. For example, both rosiglitazone and muraglitazar demonstrated superior achievement in the ability to lower blood sugar; however, these agents far from guaranteed positive patient outcomes, as they were, as it turned out, both associated with adverse CV events such as HF.<sup>1</sup>

As data emerged about positive CV outcomes in these trials, so did data demonstrating unexpected adverse effects of class agents in circulation, such as dipeptidyl peptidase 4 (DPP-4) inhibitors of the gliptin class. Nissen noted, “After 50 years of stagnation, we are now witnessing the dawning of a new era of enlightenment in pharmacological risk and benefits.”

Like many presenters at the ADA's 77th Scientific Sessions, Nissen endorsed constant updating and modification of diabetes management guidelines, specifically the ADA guidelines, to reflect contemporary knowledge gleaned from CV outcomes data of these ongoing clinical trials. "We advocated the ambitious agenda for high-quality outcome trials and benefits beyond glucose lowering," he said. "Part of what we were trying to achieve was to push regulation."

Like many colleagues also presenting at the Scientific Sessions, Lawrence A. Leiter, MD, FRCPC, FACP, FACE, FAHA, discussed how the current guidelines recommend the first-line use of metformin, but do not mention other available glucose-lowering agents that might be preferable in certain situations. Individualized diabetes management based on patient-centered factors is key, emphasized Leiter, the director of the Lipid Clinic and associate director of the Clinical Nutrition and Risk Factor Modification Centre at St. Michael's Hospital in Toronto, Ontario, Canada. A physician's job is not to uniformly prescribe "only metformin," he said. "We need to incorporate all the knowledge from these CVOTs. It is time to apply the evidence that we have learned. As endocrinologists and cardiologists, we must overcome clinical inertia to apply these favorable results to daily practice. As we observed with statins, adoption of pivotal new uses is just too slow. Close collaboration between CV and diabetes practitioners will be critical to achieve widespread adoption of new knowledge."<sup>1</sup>

### Guidelines to Reflect Cardiovascular Outcome Trials

Anne Peters, MD, professor of medicine at the Keck School of Medicine of the University of Southern California (USC) and director of the USC Westside Center for Diabetes, was among the leaders in developing the ADA's 2017 Standards of Medical Care in Diabetes. In her presentation discussing these clinical treatment guidelines, she agreed that the guidelines need to be updated at least annually to achieve better diabetes management, incorporating FDA label changes and reflecting new developments in outcome trials that utilize new agents. Guidelines, she recommended, should also integrate electronic medical records data to help with clinical decision making.<sup>2</sup>

The importance of guidelines, said Peters, is to "make it easier for [a] provider to treat the individual patient and aid them in reaching the right conclusions." The guidelines should inform and standardize patient management, "not be designed for the providers, or for the drug companies trying to promote drugs, or for health plans that use them to restrict access in choice of care," she emphasized.

"Current guidelines are too difficult to follow and need to be updated for clinical practice," said Peters. Ideally, diabetes guidelines are a "tool to help clinicians make the right decision in their own setting because we have different patients and different constraints for [each] individual patient." In reality,

“ The number of patients in outcomes trials is enormous, and we are reaping the benefits from seeds sown in 2008. ”

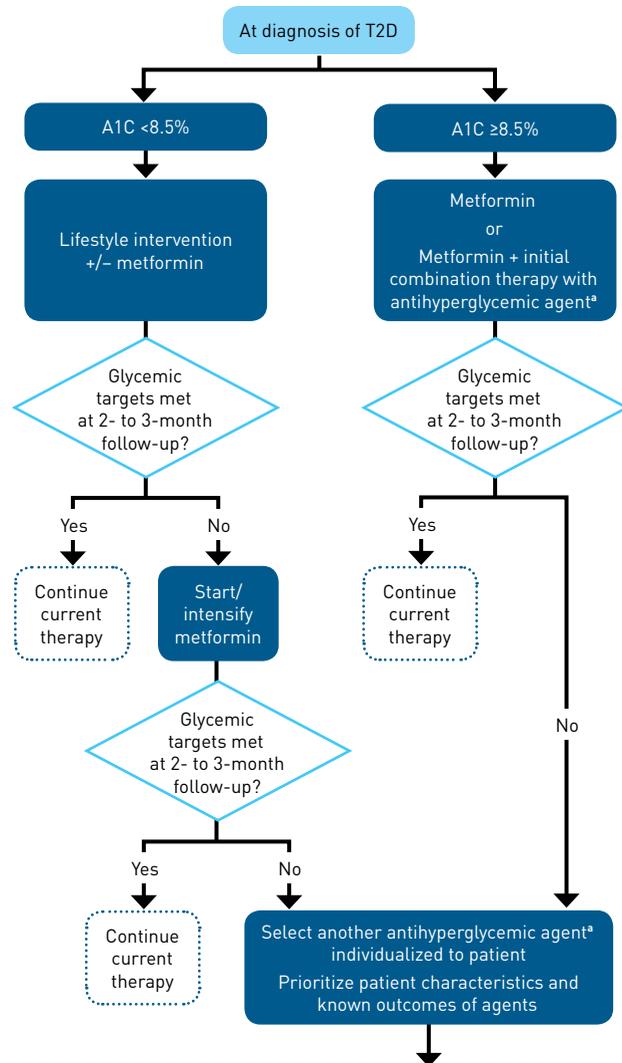
Peters acknowledged that guidelines are not perfect because they are written by endocrinology peers and group members who can disagree on treatments and who may be influenced by the patient populations they treat routinely. Through these diverse experiences and the differences among committee members, inclusion of the ability to definitively select one agent from others available may not be incorporated into the guidelines, as the panel may not always come to a consensus.<sup>2</sup>

Peters recommends that guidelines be consistent across the leading medical societies and be practical and modifiable for variable practice settings. Currently, 42 sets of guidelines, across societies, address the management of care for patients with T2D. For example, the US Preventive Services Task Force, the International Diabetes Federation's Global Guideline for T2D, and the US Department of Veterans Affairs' Clinical Practice Guidelines have all offered suggestions to modify the treatment of patients with T2D. In addition, the American College of Physicians' guidelines include only oral treatment recommendations for T2D management; their guidelines are based on systematic review and do not include data from recent CVOTs.<sup>2</sup>

As noted above, the FDA offered guidance beginning in 2008 to assess CV safety in placebo-controlled trials rather than to use comparative effectiveness with an active agent. These trials follow a large number of patients over time, providing data on measured outcomes from therapy; it is important for clinical practice guidelines to incorporate that data, said Peters. "We need to update," she stressed. "We need to do better at taking the data we have and teach primary care [practitioners] what to do because they are the ones who use these agents in practice."

The Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, updated in 2016 by the Canadian Diabetes Association (CDA), was cited as an example of well-designed guidelines. Utilizing outcomes of recent CV trials, the CDA developed a treatment scheme for individualized patient care and clinical decision making. The CDA guidelines recommend that patients with cardiovascular disease (CVD) who have unmet glycemic targets—despite treatment with metformin, insulin, or other antihyperglycemic agents—are a high-priority group. They are indicated to receive treatment with an agent in the sodium-glucose co-transporter-2 (SGLT-2) inhibitor class, because these agents have demonstrated benefits in improving CV outcomes. Intensification of treatment with additional antihyperglycemic class agents is evaluated on an

**Figure.** Factors to Determine Individualized Diabetes Management Guidelines<sup>3</sup>



PRIORITY: For patients with CVD or multiple CV risk factors	SGLT-2 inhibitor with benefit CV outcome data
Determine patient characteristics: <ul style="list-style-type: none"> <li>• Hyperglycemia</li> <li>• Risk of hypoglycemia</li> <li>• Overweight/obese</li> <li>• Comorbidities (eg, renal or hepatic condition, congestive heart failure)</li> <li>• Access and preference to treatment</li> </ul>	Considerations for class of agent* selected would be relative efficacy in the following: <ul style="list-style-type: none"> <li>• Relative A1C lowering</li> <li>• Hypoglycemic event rates</li> <li>• Weight change</li> <li>• Effect in CVOT (eg, superiority, noninferiority, not significant)</li> <li>• Dosing regimen and adverse effects</li> <li>• Cost and access</li> </ul>

A1C indicates glycated hemoglobin; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like protein-1; SGLT-2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.

\*Antihyperglycemic class agents include: alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, insulin, sulfonylureas, thiazolidinedione, weight-loss agents.

Adapted from Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes*. 2016;40(6):484-486. doi: 10.1016/j.cjcd.2016.09.003.

individual basis, with consideration recommended for factors including cost, efficacy in lowering glycated hemoglobin (A1C) levels, and clinical trial results and data, and for therapeutic considerations such as comorbidity profile, adverse effects, renal function (estimated glomerular filtration rate [eGFR]), weight, and hypoglycemic event history (FIGURE).<sup>3</sup>

Peters discussed the updated ADA guidelines for 2017. The updating committee decided to add therapeutic options based on outcomes from CVOTs: both empagliflozin, an SGLT-2 inhibitor class agent, and liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, should be considered in patients with established CVD and longstanding, suboptimally controlled T2D.<sup>4</sup> These agents have been shown to reduce CV and all-cause mortality when added to standard care. Patients with recurrent burdens of hospitalizations for CV and diabetes-related events have the greatest opportunity for benefit with these agents.<sup>2</sup> As Peters noted, “Clinically, I was impressed by the [fewer] associations with hospitalization for HF and renal events, because many of my patients in East Los Angeles have less access to care” than other populations do.

Peters reiterated that guidelines must incorporate recent CV trial findings. Any provider must find the guidelines clear and easy-to-follow, though, she noted: “Providers are judged on [their patients reaching] glycemic targets. Therefore, we must be sensitive to [the] need for clear guidance regarding A1C reduction. Remember the need for statin and blood pressure-lowering agents in addition to—but not in spite of—these new treatments.”

Peters highlighted the potential need to recommend additional diabetes medications in patients with CVD and potential nephropathy. “Metformin is first-line therapy, and it will stay around as first-line either as monotherapy or in dual therapy.” For patients who are intolerant to metformin, she recommended drugs for second-line or first-line therapy that have established CV benefit, as follows:

- An SGLT-2 inhibitor, if the patient has an eGFR >45
- A GLP-1 RA, if the patient’s lack of eGFR indicates little renal risk

### Conclusion

In short, therapy choice should always be individualized for each patient. In the subset of patients with T2D with established CVD, evidence-based guidelines can offer additional considerations. For example, for patients who are very lean or have lost too much weight on some therapies, clinicians should monitor body weight and incorporate these types of considerations in the appropriate management selection of guidelines. Additionally, patients with renal insufficiencies may preferentially benefit from agents identified through outcomes shown in CVOTs to have positive results. Clinicians and those who are responsible for preparing guidelines need to include study findings from CVOTs in their recommendations for the

integration of multidisciplinary treatment strategies for patients living with these comorbidities. ●

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## New SUSTAIN 6 Trial Insights: Retinopathy Complications of Semaglutide

The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trials evaluated the efficacy and safety of semaglutide administered subcutaneously in patients with type 2 diabetes (T2D). Semaglutide is a once-weekly investigational human glucagon-like peptide-1 receptor agonist (GLP-1 RA) that stimulates insulin and suppresses glucagon secretion in a glucose-dependent manner, while decreasing appetite and food intake. Across 6 trials, semaglutide was investigated for glucose-lowering effects compared with placebo, sitagliptin, exenatide extended-release, insulin glargine as add-on therapy to insulin, and placebo in addition to standard of care treatment (TABLE 1).<sup>1</sup>

At the American Diabetes Association (ADA) 77th Scientific Sessions, Stephen C. Bain, MD, professor of medicine at the School of Medicine, Swansea University, United Kingdom, presented results demonstrating that semaglutide had greater efficacy in consistently reducing glycated hemoglobin (A1C) and body weight than comparators, in 3918 patients with T2D enrolled in the SUSTAIN 1 to SUSTAIN 5 trials.<sup>1</sup> These trials demonstrated that semaglutide was associated with substantial glucose-lowering effects. A greater proportion of patients achieved target A1C <7%

with semaglutide; this extended to patients with baseline A1C >9% who achieved target glucose levels with semaglutide (FIGURE).<sup>1</sup>

### SUSTAIN 6 Trial

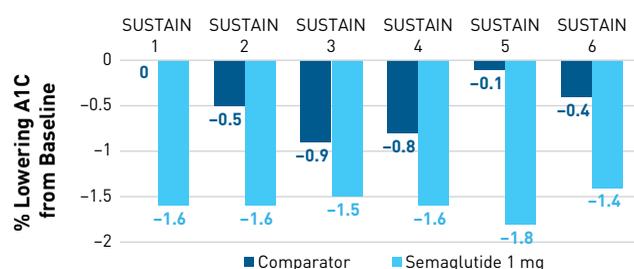
The SUSTAIN 6 trial was designed to establish noninferiority to placebo in prevention of cardiovascular events in patients with T2D who have established cardiovascular risk. At the American Diabetes Association 77th Scientific Sessions, Tina Vilsbøll, MD, DMSc, presented an analysis of adverse microvascular events from SUSTAIN 6, which explained the worsening retinopathy associated with the investigational semaglutide treatment. Vilsbøll, the chief consultant endocrinologist, Department of Medicine, and director of the Center for Diabetes Research at Gentofte Hospital, University of Copenhagen, Denmark, suggested that retinopathy was associated with rapid glucose-lowering in patients already vulnerable to the complication. Vilsbøll stressed the significance of assessing all of the trial's results, especially in investigational agents. She said, "[It is] important for us, as clinicians, to look at all other outcomes that come from this trial. We enrolled a lot of patients and treated them over time with a compound not yet on the market."<sup>2-</sup>

**Table 1.** SUSTAIN 1-SUSTAIN 6 A1C Improvement With Semaglutide Versus Comparators<sup>1,3</sup>

Trial	Study population	Design	Glucose-lowering efficacy
SUSTAIN 1	N = 388 treatment-naïve with T2D	30-week; semaglutide vs placebo	Reductions from baseline A1C (mean: 8.1%): 1.6% 1-mg semaglutide vs <0.1% placebo
SUSTAIN 2	N = 1231 with T2D	56-week; semaglutide vs sitagliptin 100 mg once daily as add-on to metformin and/or sulfonylurea or thiazolidinedione	Reductions from baseline A1C (mean: 8.1%): 1.6% 1-mg semaglutide vs 0.5% 100-mg sitagliptin
SUSTAIN 3	N = 813 with T2D	56-week; semaglutide vs exenatide extended release 2 mg once weekly as add-on to 1-2 oral antidiabetic drugs	Reductions from baseline A1C (mean: 8.3%): 1.5% 1-mg semaglutide vs 0.9% 2-mg exenatide extended release
SUSTAIN 4	N = 1089 insulin-naïve with T2D	30-week; semaglutide vs insulin glargine once daily as add-on to metformin with or without sulfonylurea	Reductions from baseline A1C (mean: 8.2%): 1.6% 1-mg semaglutide vs 0.8% insulin glargine
SUSTAIN 5	N = 397 with T2D	30-week; semaglutide vs placebo as add-on to basal insulin alone or basal insulin in combination with metformin	Reductions from baseline A1C (mean: 8.4%): 1.8% 1-mg semaglutide vs 0.1% placebo
SUSTAIN 6	N = 3297 with T2D with 83% established CVD and/or CKD	104 week; semaglutide vs placebo in addition to standard of care	Reductions from baseline A1C (mean: 8.7%): 1.4% 1-mg semaglutide vs 0.4% placebo

A1C indicates glycated hemoglobin; CKD, chronic kidney disease; CVD, cardiovascular disease; T2D, type 2 diabetes.

**Figure.** Glucose-Lowering Efficacy Across SUSTAIN Trials<sup>1</sup>



A1C indicates glycated hemoglobin.

In the SUSTAIN 6 trial, a total of 3297 patients with diabetes were randomized to once-weekly treatment with subcutaneously administered semaglutide at dosage of 1 mg or 0.5 mg or placebo for 2 years. Much like other CV outcomes trial designs, enrolled patients aged 50 years or older had established cardiovascular disease (CVD) or chronic kidney disease, while patients 60 years of age and older had at least 1 cardiovascular risk factor. The entire patient population had long-lasting T2D disease (mean: 13.9 years), and it was uncontrolled, with an A1C >7% (mean: 8.7%) despite treatment with up to 2 oral antidiabetic agents. The glucose-lowering medication introduced during the trial was primarily insulin; in addition, non-insulin glucose-lowering medication was used, such as sodium-glucose cotransporter 2 inhibitors at end of trial. At time of randomization, 98.1% of the population had been receiving medication to treat CVD.<sup>3</sup>

The primary outcome was the composite 3-point major adverse cardiac events (MACE) outcome of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. For the primary end point, semaglutide met criteria for noninferiority compared with placebo treatment ( $P < .001$ ); time to first occurrence of MACE occurred at a rate of 6.6% in the semaglutide group compared with 8.9% in the placebo group over the 2-year trial period. The SUSTAIN 6 trial demonstrated that semaglutide reduced the primary composite MACE end point by 26% compared with placebo; as such, in order to prevent 1 cardiovascular-related death, nonfatal MI, or nonfatal stroke, 45 patients would need to be treated with semaglutide for 2 years. SUSTAIN 6 also demonstrated that semaglutide significantly reduced the expanded composite outcome, including death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization or hospitalization for unstable angina, or HF compared with placebo (HR, 0.74; 95% CI, 0.62-0.89;  $P = .002$ ). However, semaglutide demonstrated no benefit in reduction of all-cause mortality or cardiovascular death end points alone, compared with placebo.<sup>3</sup>

### Glucose-Lowering Efficacy

Patients treated with semaglutide achieved significantly greater glycemic control at either drug dose than patients receiving

**Table 2.** Retinopathy Complication Rates from SUSTAIN 6<sup>3</sup>

	Semaglutide	Placebo	HR	P
Total retinopathy complications	50	29	1.76	.02
Need for retinal photocoagulation	38	20	1.91	.02
Vitreous hemorrhage	16	7	2.29	.07
Need for treatment with intravitreal agent	16	13	1.23	.58
Onset of diabetes-related blindness	5	1	5.01	.14

HR indicates hazard ratio.

placebo. At week 104 of the trial, the 1-mg dose of semaglutide decreased A1C 1.4% from the baseline mean A1C of 8.7%. Compared with placebo treatment, patients achieved a relative reduction of 1.05% from baseline A1C (95% CI, -1.19 to -0.91;  $P < .0001$ ) with either dose of semaglutide. Insulin usage was more than 2-fold higher in the placebo arm than the treatment arm, while severe or symptomatic hypoglycemic adverse event (AE) rates were similar across treatment groups.<sup>3</sup>

Semaglutide treatment was associated with a mean decrease in body weight of 4.5 kg from the baseline 92.1 kg, with weight loss reaching a plateau at approximately 44 weeks of the trial. Gastrointestinal (GI) disorders including diarrhea, nausea, and vomiting occurred in an average of 51.5% and 35.4% of patients in the treatment and placebo arms, respectively.<sup>3</sup>

The high incidence of nausea and vomiting in the treatment arm was at first believed to be related to weight loss associated with use of semaglutide. However, in an additional cohort analysis presented by Vilsbøll at the ADA 77th Scientific Sessions, GI-related AEs were not associated with body weight loss. Patients were split into cohorts based on GI symptoms. From baseline to week 104, patients with GI symptoms of diarrhea, nausea, or vomiting achieved a 3.9% decrease in body weight compared with a 4.8% decrease in patients without these symptoms. Moreover, semaglutide-related AEs lead to discontinuation in 13% of patients, driven by higher rates of nausea, vomiting, and diarrhea.<sup>2</sup>

Semaglutide decreased the rates of new or worsening nephropathy; 6.1% of placebo-treated patients ( $n = 100$ ) and 3.8% of semaglutide-treated patients ( $n = 62$ ) experienced new or worsening nephropathy ( $P = .005$ ). However, results from SUSTAIN 6 demonstrated that semaglutide, compared with placebo, was associated with adverse microvascular safety outcomes and increased diabetic retinopathy complications. Diabetic retinopathy was defined by the need for treatment with retinal photocoagulation or intravitreal agents with a diagnosis of vitreous hemorrhage, or onset of diabetes-related blindness. Over the trial period, diabetic retinopathy complications occurred at a significantly higher rate in the semaglutide arm than with placebo: 50 patients (3%) receiving semaglutide compared with 29 patients receiving placebo treatment (1.8%) developed diabetic retinopathy complications (HR, 1.76; 95% CI, 1.11-2.78;  $P = .02$ ).<sup>3</sup>

Additionally, 66 patients (83.5%) in the semaglutide arm and 24 patients (82.8%) in the placebo arm with retinopathy complications had preexisting retinopathy at baseline. Of the 79 patients with retinopathy complications in the semaglutide arm, 38 patients (2.3%) required retinal photocoagulation compared with 20 patients (1.2%) in the placebo group. Intravitreal agent injections were required in 16 patients in the semaglutide arm (1%) and 13 (0.8%) patients in the placebo group. Vitreous hemorrhage occurred in 16 (1%) versus 7 (0.4%) patients, and diabetes-related blindness in 5 (0.3%) patients versus 1 (0.1%), in the semaglutide group and the placebo group, respectively. (TABLE 2).<sup>3</sup>

### New Analysis of Cohort with Retinopathy Outcomes

Following the publication of the results of the SUSTAIN 6 trial, peer investigators requested further analysis in Letters to the Editor in the *New England Journal of Medicine* for guidance on how clinicians can treat patients with retinopathy and with baseline A1C high enough to be susceptible to the rapid glucose-lowering effects of semaglutide.<sup>4,5</sup> Investigators explored the association between high A1C at baseline and progression of diabetic retinopathy to offer insights into treatment with semaglutide.

In an extended analysis of the patient population experiencing retinopathy, presented at the ADA 77th Scientific Sessions, Vilsbøll provided possible reasons for this imbalance (TABLE 3).<sup>2</sup> Compared with the overall population, patients experiencing retinopathy events had worsened glycemic control and additional retinopathy complications at baseline. Moreover, all patients experiencing rapid A1C lowering during the trial developed additional retinopathy complications.<sup>2</sup>

In discussing an evaluation of the 79 patients with confirmed events of retinopathy, Vilsbøll emphasized the characteristic differences in these patient populations. Patients with retinopathy complications had more advanced diabetes compared with the overall treatment population, indicated by a longer duration of diabetes diagnosis (17.5 years vs 13.9 years). Additionally, patients with retinopathy events had a greater dysregulation of glucose control, with an average A1C of 9.4% compared with 8.7% in the overall patient group. Higher insulin usage was identified in the cohort with retinopathy complications compared with the total population (75.9% vs 58%, respectively).<sup>2</sup>

Overall, 83.5% of the patient cohort with confirmed retinopathy events had history of diabetic retinopathy compared with 29.4% of patients in the overall population. Furthermore, a greater proportion of patients experiencing retinopathy events during the trial had a history of proliferative retinopathy (29.1% vs 6.1%) and previous treatment with laser therapy or intravitreal agents for proliferative retinopathy (17.7% vs 3.4%) compared with the total population. In the patients without a history of diabetic retinopathy, the risk of developing retinopathy complications was low and comparable in the placebo and semaglutide treatment groups.<sup>2</sup>

**Table 3.** Comparative Baseline Characteristics in Patients with Retinopathy Complications in SUSTAIN 6<sup>2</sup>

	Total population	Retinopathy cohort
Duration of diabetes	13.9 years	17.5 years
A1C at baseline	8.7%	9.4%
History of retinopathy	29.4%	83.5%
History of proliferative retinopathy	6.1%	29.1%
Previous treatment with intravitreal agents/laser therapy for proliferative retinopathy	3.4%	17.7%

A1C indicates glycated hemoglobin.

When evaluating the overall population in comparison with patients with retinopathy events, patients with a retinopathy event initiated treatment with a higher A1C at baseline and experienced a greater decrease in A1C nearly immediately, at 16 weeks. Retinopathy complications were found to be higher in those patients with preexisting retinopathy at baseline and with greater A1C reductions at week 16; patients with an A1C decrease by week 16 of more than 1.5% had a higher risk than patients with a decrease of 0.5% in A1C. Vilsbøll indicated that data are consistent with early worsening of diabetic retinopathy associated with rapid improvement in glycemic control, such as that seen with insulin.<sup>2</sup>

An attendee at the session questioned whether an FDA-required black box warning or strong language should be associated with semaglutide usage, as with canagliflozin, despite a “2-fold increased risk of amputations and low frequency of events for amputations.” Vilsbøll responded that, unlike the black box indication for pancreatitis with GLP-1 RA treatment, the retinopathy risk is better understood for semaglutide. She noted, “In contrast to the black box warning for pancreatitis where we didn’t understand much, we understand more about the drivers behind complications. With data demonstrated today [on diabetic retinopathy complications], clinicians have a good explanation: Risk is established in the population with long-standing disease and vulnerability to retinopathy complications, and have received laser therapy or intravitreal agents. As a clinician, this data offers a good explanation for how to apply careful treatment in patients at risk.”<sup>2</sup> ●

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## Prediction of Readmission Risk to Reduce Diabetes-Related Hospitalizations

At the 77th Scientific Sessions of the American Diabetes Association (ADA), Daniel J. Rubin, MD, MSc, FACE, led a session that demonstrated how quantitative and qualitative studies can provide insight into multifactorial, complicated risk factors for diabetes-related readmissions. In addition, Rubin, an associate professor of medicine at the Lewis Katz School of Medicine and chair of the Glycemic Control Taskforce, Temple University Hospital, Philadelphia, identified unmet needs in care that may help develop strategies to reduce readmissions.<sup>1</sup>

Diabetes-related complications account for 23% (8.8 million) of all annual US hospitalizations, and patients with diabetes are at increased risk for hospital readmissions. Approximately 20% of index hospitalizations of patients with diabetes are followed by a readmission within the first 30 days post hospitalization. The 30-day readmission rate for all hospitalized patients is 8.5% to 13.5%; for those with diabetes, it is 14.4% to 21.0%.<sup>2</sup>

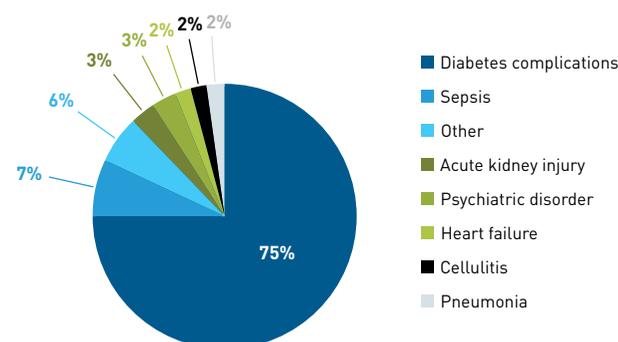
Reducing hospital readmission rates is a high-priority target for diabetes management. In 2012, annual hospital care expenditures in the United States for patients with diabetes totalled \$125 billion.<sup>3</sup> Between 27% and 35% of all patients with diabetes will have multiple hospitalizations within a given year. Moreover, patients with multiple hospital admissions who have diabetes as the primary diagnosis are associated with costs that are 3 times higher than patients without diabetes with 1 hospitalization (\$23,100 vs \$8500).<sup>1</sup>

An analysis of hospital readmission trends from 2009 to 2013 in the Healthcare Cost and Utilization Project Statistical Brief showed that, in 2013, nearly 500,000 index admissions were associated with diabetes complications. In addition, the all-cause 30-day readmission rate for this patient group was 20.4% (n = 99,108), with total costs coming to \$1.204 billion.<sup>3</sup>

Readmissions within 30 days of discharge of index hospitalization are, in general, often the target for care programs. As all-cause readmissions account for approximately \$26 billion annually in Medicare spending, CMS has focused on specific practice patterns that may contribute to unnecessarily high readmissions costs. The Affordable Care Act established the CMS Hospital Readmissions Reduction Program to financially incentivize the reduction of preventable readmissions by encouraging hospitals to improve quality care.<sup>3</sup> In short, “hospital readmissions, especially within 30 days, are looked [at] as a failure of care,” stated Rubin.

Numerous factors contribute to this failure of care, including inadequately relayed information on the part of the hospital, medical errors during treatment, or inappropriate follow-up of care. On the patient side, poor compliance, poor adherence to the appropriate care plan provided by the clinician, lack of support from caregivers, and deterioration of clinical condition can also contribute to rehospitalization.<sup>1</sup>

**Figure 1.** 30-Day Readmission Diagnosis After Index Hospitalization for Diabetic Ketoacidosis<sup>4</sup>



### Recurrent Admission for Diabetic Ketoacidosis

Hospitalizations for diabetic ketoacidosis (DKA) result in US medical expenditures of more than \$2.4 billion annually. In 2009, approximately 140,000 patients were discharged from a hospital with a diagnosis of DKA. DKA is the most common cause for readmission for those patients discharged with a diagnosis of DKA, and is, therefore, a challenge to current care.<sup>4</sup>

A retrospective study evaluated 268 patients with recurrent DKA hospitalizations to assess risk factors for readmission in this population. Within 5 years of index admission for DKA, 58 patients had more than 1 readmission. In order to determine risk factors associated with readmissions, 40 patients with index admission for DKA, but no readmissions for DKA, were matched with 40 patients with readmissions, to compare factors including age, gender, ethnicity, and duration of diabetes.<sup>5</sup>

Investigators found that the readmission group had DKA events that were more severe, eg, the patient cohort with readmissions had a mean pH reading of 7.12, compared with 7.17 in the cohort with a single hospitalization for DKA. The readmissions cohort also had worse glycemic control than did the nonreadmission cohort, measured by glycated hemoglobin (A1C), with A1C means of 11.4% versus 9.8% ( $P = .014$ ). However, no other differences were identified between the readmission group and nonreadmitted patients; both groups had similar rates of omission of insulin usage, missed visits to post care clinics, and alcohol abuse.<sup>5</sup>

A larger study presented at the ADA's 77th Scientific Sessions by Katherine Lopez, MD, revealed significant risk factors in the population of patients with 30-day readmissions following an event of DKA. Using the 2014 National Readmission Database, Lopez, of Mount Sinai St Luke's, New York, identified adult patients with hospital readmission following an episode of DKA (FIGURE 1<sup>4</sup>). Of 106,587 total admitted patients, 47,809 were admitted with DKA. Of those 47,809, approximately 13%

(n = 6235) were subsequently readmitted within 30 days of index. Investigators identified significant risk predictors of readmission for DKA, including end-stage renal disease and a Charlson Comorbidity Index score of more than 3 (FIGURE 2).<sup>4</sup> These predictors increased 30-day readmission risk rates 2-fold.

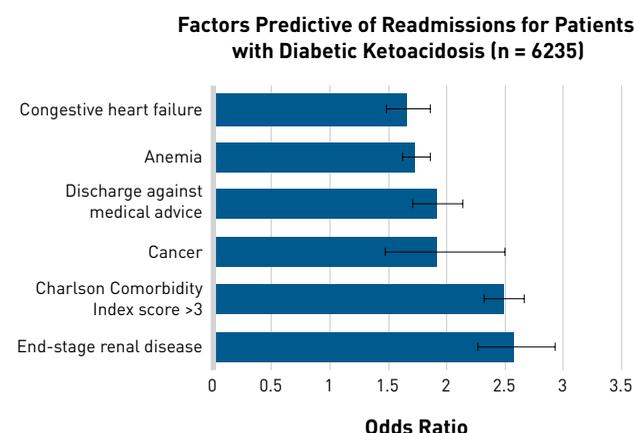
The Charlson Comorbidity Index contains 19 categories of comorbidity that help predict the 10-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, which identifies mortality risk of the respective condition (such as myocardial infarction, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, connective tissue disease, peripheral vascular disease, renal disease, diabetes [with and without end organ damage], cancer, etc).<sup>4,6</sup>

### Quantitative Risk Factors for Diabetes-Related Readmissions

Rubin also presented his team's work on the Diabetes Early Readmission Risk Indicator (DERRI) tool at the ADA's 77th Scientific Sessions. DERRI is used to predict risk of 30-day readmission using markers of risk for all-cause readmission among hospitalized patients with diabetes. In his retrospective study, Rubin identified 44,203 patients with diabetes who had been discharged from an academic medical center. Of these patients, 20.4% (n = 9034) were readmitted to the hospital within 30 days following discharge. The most common readmissions were attributed to diabetes, heart failure, procedural complications, shortness of breath, acute kidney failure, and urinary tract infection.<sup>7</sup>

Using DERRI, 10 statistically significant ( $P < .001$ ) predictors were identified as risk factors in patients hospitalized with diabetes (TABLE 1<sup>7,8</sup>). Complications of diabetes were reported as predictors of readmission within 30 days following index hospitalization. Of the patients readmitted within 30 days, 30% had at least 1 microvascular complication and 56% had 1 or more macrovascular complications. Patients with 4 macrovascular complications, including coronary artery disease, heart failure, stroke, and peripheral vascular disease, had the highest predictive association with readmission (odds ratio [OR], 1.43; 95% CI, 1.04-1.96;  $P = .026$ ). In addition, preadmission insulin use was a significant predictor of 30-day readmission risk; in fact, 50.2% of patients who were discharged, then readmitted within 30 days, had preadmission use of insulin prior to index hospitalization (OR, 1.25;  $P < .0001$ ). Any employment status other than employed was also predictive of readmission risk. Patients with the employment status of "disabled" had a nearly 2-fold increased risk of 30-day readmission (OR, 1.94; 95% CI, 1.63-2.32;  $P < .0001$ ). Interestingly, patient residence within 5 miles of the hospital was associated with higher readmission rates, compared with patients who lived farther from hospitals, among patients with diabetes.<sup>7</sup>

**Figure 2.** Factors Predictive of Readmissions for Patients with Diabetic Ketoacidosis (n = 6235)<sup>4</sup>



**Table 1.** Early Readmission Risks in Patients with Diabetes Using Predictive DERRI Tool<sup>7,8</sup>

Predictive factor	OR	95% CI	P
Disabled (vs employed)	1.94	1.63-2.32	<.0001
Discharged 90 days before admission	1.93	1.76-2.11	<.0001
Discharge against medical advice 1 year before admission (vs home discharge)	1.49	1.05-2.10	.024
4 macrovascular complications (vs 0 macrovascular complications)	1.43	1.04-1.96	<.026
Insulin use preadmission	1.25	1.14-1.36	<.0001
Anemia	1.26	1.15-1.39	<.0001
A1C <6.5% (vs 6.5%-8%)	1.07	1.02-1.13	.012
Cholesterol <150 mg/dL (vs 150-200 mg/dl)	1.06	1.00-1.11	.03

A1C indicates glycated hemoglobin; DERRI, Diabetes Early Readmission Risk Indicator; OR, odds ratio.

A hospital discharge within 90 days before admission was associated with a readmission rate of 52.5% compared with a 27% rate of those not readmitted. Patients who were discharged within 90 days prior to initial admission had a nearly 2-fold higher predictive risk of readmission within 30 days of discharge (OR, 1.93; 95% CI, 1.76-2.11;  $P < .0001$ ). In addition, patients with the most recent discharge status of "leaving against medical advice," up to 1 year prior to admission, had the highest 30-day readmission risk compared with other discharge statuses (OR, 1.49; 95% CI, 1.05-2.10;  $P = .024$ ).<sup>7</sup> Prior to this study, levels upon index admission of serum hematocrit, creatinine, and sodium had not been identified as predictors of 30-day readmission risk, but studies have demonstrated that burden of comorbidities is associated with readmission. In line with previous studies, patients with a diagnosis of anemia had a higher risk of 30-day readmission.<sup>7</sup>

In an extended analysis of the DERRI tool, Rubin showed that glycemic control and lipid levels are significantly associated with 30-day readmission risk, in addition to the 10 previously

**FIGURE 3.** Qualitative Early Readmission Risks in Patients with Diabetes<sup>2</sup>

Failure of protective factors, such as:

- › Awareness of medication changes upon discharges
- › Adequate supportive social network
- › Loss of control over illness
- › Poor health literacy
- › Health system failure
- › Social determinants of health impeding care, such as:
  - Limited transportation
  - Lack of income to afford appointments or to obtain medication
  - Lack of caregiver's help to follow discharge plan
  - Psychological withdrawal

identified predictive risks. Rubin retrospectively identified 105,974 patients with type 2 diabetes previously discharged from 2 academic centers. Of the discharged patients, 19,062 had 30-day readmissions (18%). In this extension, patients with lower A1C, defined as below 6.5%, had higher odds of early readmission compared with patients with A1C levels between 6.5% and 8% (OR, 1.07; 95% CI, 1.02-1.13;  $P = .012$ ). Patients with total cholesterol levels lower than 150 mg/dL had a higher risk of readmission compared with patients with cholesterol levels between 150 and 200 mg/dL (OR, 1.06; 95% CI, 1.00-1.11;  $P = .03$ ).<sup>8</sup>

Most 30-day readmissions occurred early after discharge; the median time to readmission was 11.2 days. Predicting readmission risk and implementing strategies through an electronic tool, according to Rubin, may be used at point-of-care at index hospitalization to help prevent subsequent hospitalizations. Rubin noted the importance of timing and that it's crucial to have a treatment strategy at the time of discharge while they are still in the hospital and a plan for a 1-week follow up to prevent unnecessary hospitalization. Early intervention, he said, is important because "if you wait too long to do your outreach and try to keep patients from coming back, it's too late. We need to do this [at] point-of-care before they leave the hospital and within the first week."

Rubin and his team are currently investigating approaches to implement the DERRI-CVD tool to determine predictive factors of risk of 30-day readmission in patients with diabetes who are hospitalized for cardiovascular disease (CVD). Another retrospective analysis conducted by Rubin of patients with diabetes ( $n = 8189$ ) had results similar to that of the DERRI study, identifying all the same predictive factors for readmission risk.<sup>1</sup>

Rubin reiterated that the DERRI tool can be used to identify those patients at higher risk of 30-day readmissions during the course of a hospitalization. This would allow clinicians to be better equipped to introduce interventions, prior to discharge, to reduce readmission risk.<sup>7</sup>

### Qualitative Risk Factors of Readmission

Although tools such as DERRI can help calculate quantitative risk factors, Rubin also highlighted the complexity of readmissions predictions. Others factors can include socioeconomic status, demographic characteristics, and health status, as well as hospital care, hospital-based care characteristics, postdischarge activity, and transition of care.

Rubin presented data from another investigation to underscore the qualitative factors potentially predictive of hospital readmission risk. In this study, Rubin explored patient-reported explanations for readmission in 20 adult patients with diabetes who were readmitted within 30 days following hospitalization.<sup>2</sup>

Several themes emerged as major risk factors for hospital readmission for diabetes-related illness (FIGURE 3<sup>2</sup>). Patients reported a great deal of education barriers: they lacked understanding of diabetes as a chronic disease, including pathology and appropriate management; they had poor health literacy, impeding effective management; they had difficulty understanding discharge instructions; and they demonstrated a lack of understanding of the importance of A1C measures.

Most of the 20 patients included in the study denied having a role in exacerbating their condition prior to readmission, believing that readmission, as well as diabetes and any associated medical illnesses, were "out of [their] control." Although patients indicated that they had the resources required to recover, including family and social support, a majority were readmitted for the same condition as index. Most patients reported that, after discharge, they required assistance with transportation, obtaining and taking medications, and preparing food.<sup>2</sup>

These patients reported that their discharge process and postdischarge support were inadequate. Although most patients reported that they understood and followed discharge instructions and remembered the material, many were readmitted anyway. However, some patients reported obstacles to following the medical plan post discharge.

In this study, Rubin had identified inpatient diabetes education and inpatient glycemic control as expected protective factors against readmission; however, these failed to prevent readmission as expected. Rather, the study found that it was other factors that were better predictors of readmission, such as: the failure of the patient to follow discharge instructions; the failure of the patient to be aware of medication changes upon discharge; the lack of help, support, and other social determinants; and the loss of control over their illness.

### Conclusion

Hospitalizations for diabetes and diabetes-related complications, including DKA, pose significant burdens to the US healthcare system. The high rate of costly 30-day readmissions is especially burdensome. Valuable studies were presented at the ADA's 77th

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## Remote Monitoring of A1C in Type 1 Children and Adolescents With Diabetes Improves Clinical Outcomes

At the 77th Scientific Sessions of the American Diabetes Association (ADA), Deneen Vojta, MD, executive vice president of research and development at UnitedHealth Group in Minnetonka, Minnesota, moderated a discussion regarding the current state of type 1 diabetes (T1D) management in adolescent patients and how utilization of technology can improve patient care. Through remote monitoring via connected devices, physicians can individualize care for patients with T1D. However, physicians can face challenges in implementing remote monitoring, Vojta explained: “Face-to-face patient education is labor-intensive, urgent management on the telephone is not reimbursed [by insurance], manual review of uploaded pump and meter data is time-intensive, and lack of best-practice protocols allows for inconsistent refills of medication [and] inconsistent reimbursement.”<sup>1</sup>

Frequent monitoring of glycated hemoglobin (A1C) is crucial to patient care, as A1C is a measure of average blood sugar levels over the past 2 to 3 months. Controlling blood glucose and lowering A1C, even for short periods of time, are associated with better long-term health outcomes. However, current care is based on retrospective review, where patients may be seen infrequently and appointments may be erratic. Vojta noted the potential burden on a family who may be involved in visiting a nonlocal physician with a child 4 times a year: planning the trip, missing work, a long drive to the hospital. Because of these barriers, and often others, struggling families are not monitoring or uploading data from glucose meters, insulin pumps, and continuous glucose monitoring (CGM) systems.<sup>1</sup>

Pediatric endocrinologist Laura Gandrud, MD, noted that typically, “Nonadherent families are struggling to manage a difficult disease. Teens, [for instance,] are only testing [blood glucose] once a day.” Gandrud, of Children’s McNeely Pediatric Diabetes Center, with locations in Minneapolis and St. Paul, Minnesota, said that these trends in nonadherence continue outside the McNeely Center, which serves nearly three-quarters of the children with T1D in that metropolitan area. In fact, an analysis of patient data collected between September 2013 and December 2014 from the T1D Exchange Clinic Registry demonstrated the current state of T1D treatment and management, nationally. In US adolescents, the level of diabetes control is deteriorating, there is lower penetration of new devices for CGM and the teens have a higher burden of mental health disorders. Just 17% to 23% of patients with T1D younger than 18 years had met the ADA goal for A1C <7.5%. Patients 13 to 17 years had a mean A1C of 9.0%, demonstrating great need for better control. In patients younger than 18 years (n = 8463), only 6% were using

“Connected devices and frequent support improve quality of life for patients with T1D.”

a CGM for management, compared with 16% among those 18 and older. Patients of all ages, but especially the youngest, would benefit from wider adoption of technology.<sup>2</sup>

Working with UnitedHealth Group, Gandrud designed a pilot study for adolescent patients with T1D, hypothesizing that frequent, intensive monitoring of blood glucose would significantly reduce A1C levels. Weekly digital communications would analyze blood glucose trends. A total of 117 pediatric patients with T1D were recruited between September 2015 and March 2016 from the Children’s McNeely Pediatric Diabetes Center; these patients had A1C levels and glucose control similar to those of the patients in the T1D Exchange study. The McNeely patients were using an insulin pump with or without a continuous glucose sensor, had been diagnosed with diabetes for at least 1 year, and had been seen in a clinic within 6 months prior to enrollment. They were testing blood glucose levels at least 3 times a day, and they were not controlled on insulin, with baseline A1C levels between 8% and 10.5%.<sup>1</sup>

Patients were randomized to conventional care (n = 57) or intensive remote therapy (IRT) (n = 60) for a 6-month care-focused intervention program. In the IRT cohort, patients continued regular quarterly planned clinic visits, and they downloaded pump and Fitbit data on a weekly basis using smartphone apps such as Glooko, Medtronic, or CareLink, depending on compatible software. Clinicians reviewed the study data weekly, and then recommended changes in variables, such as timing and dosing of insulin, as well as lifestyle changes. Patients had regular contact with providers through phone or email, in which the therapy summary was sent to the patient after review by a provider; patients also received appointment notifications and reminders to upload data. In a typical patient correspondence, positive reinforcement came first, stating “Keep up the good work!” That was followed by recommendations on changes to basal rate and by treatment scheduling, as needed.

Patients in the control group continued with regular visits, and uploaded their data weekly, as the IRT group did, via Fitbit, CareLink, or other software. However, the clinical team did not review the data of the control-group patients and no additional contacts were made apart from appointment reminders and their regular quarterly visits. No extra “touchpoints” of care by the physician were experienced by the control-group patients.

The primary outcomes of this study were changes in A1C from baseline to the point reached after 6 months of intervention. Intervention stopped after visit 3, but the study continued for 3 months (for a total of a 9-month study period) after the cessation of contact in order to evaluate any effects that lasted after remote communication ended.

For patients of all ages, those with IRT had a greater improvement in A1C from baseline to 6 months, with a decrease of 0.34% compared with 0.05% in the control group. Interestingly, the study results revealed that the older patient cohort (adolescents aged 13 to 17 years) may need the most support for successful management of T1D. Intensive remote monitoring was most effective among older children; during the study, these patients took full advantage of the program, yielding A1C reductions of 0.84% over 6 months. Overall, frequent communication in the group with IRT was more effective in children who downloaded their data more frequently (at least 20 times per week). Investigators found that a critical hit, or plateau effect, was observed at 20 weeks or more, which necessitated the need for intervention by clinicians. While A1C decreased 0.70% in the IRT cohort with 24 weeks of downloads, the decrease was just 0.08% among those who had participated for 20 or fewer weeks.

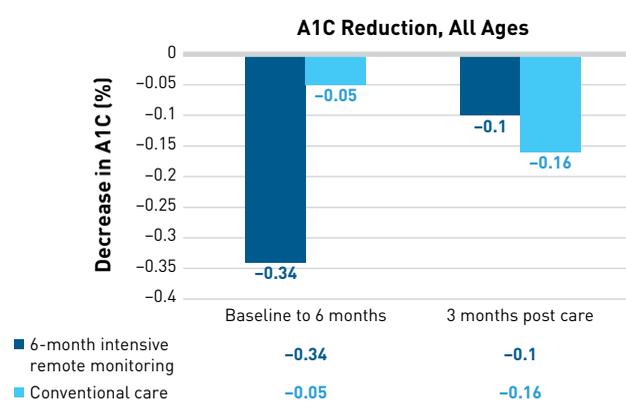
After 6 months of intervention with weekly contact with the physician in response to data uploads, the patients went 3 months without this contact. The subsequent changes in A1C, from 6 months to 9 months, reflect the importance of intervention for this patient group (FIGURE 1). In the group aged 13 to 17 years, the change in A1C 3 months post intervention was still down from baseline by 0.22%, compared with 0.17% in the control group. Across all age groups, the change from 6 months to 9 months was down from baseline 0.10% in the IRT group, and 0.16% in the control group. Continued care is recommended as it had led to improvements in lowering A1C.

Connected devices and frequent support improve quality of life for patients with T1D. Patients involved in the pilot study had a high rate of data upload, supported by automated text reminders; investigators noted that passive upload to the cloud will improve this outcome in the future. The high rate of adherence was also positively affected by the support afforded by the study: contracted technology support for these patients ensured operability and data visualization. Typically, there are many obstacles and challenges to data uploading because data exists on multiple devices, each often with different software platforms for installation and uploading. In the study, the IRT group benefited from having consumer tech support for connectivity issues.

### Limitations

In a session open to audience questions, 1 endocrinologist challenged the utility of such practices, emphasizing the substantial burden on the physician and healthcare facility to analyze the

**Figure.** Cessation of Intensive Remote Monitoring Adversely Affects Glucose-Lowering<sup>1</sup>



data with no reimbursement for the time required to do so. For the 60 patients in this trial, data management was handled by a full-time certified diabetes educator, who reviewed data, and by a part-time nurse practitioner; investigators noted they will not have the resources to continue to manually review data. The future of data management will be an analytic program developed for patients, who will then upload data from home; the program will scan all data and identify red flags in readings. However, integrated data visualization is needed for providers, such as graphs and other reports; researchers visualizing data must have 3 screens for displaying data for activity, as well as the data from pumps and sensors. Programs need data integration to improve efficiency; the adoption of software platforms in the clinic can help families sort out data-uploading obstacles.<sup>1</sup>

Investigators and attendees noted the need for an automated process to prevent data overload; eventually, data will be automatically uploaded and strategies and suggestions for changes in self-management (eg, dosing) will be given in real time. Vojta indicated that family doctors might one day outsource the data analysis that is involved in more frequent monitoring, or that computer software may be developed to analyze data in real time, which could alert the doctor when a troubling change in the patient's vital signs is detected.<sup>1</sup>

### Payment Redesign Is Key

What will it take to make automated monitoring available nationally? The easiest part of this shift in treatment is the manufacturing of devices and of the middleware to link the data on the patient and provider ends. Many companies are developing and commercializing these technologies for patients with diabetes. The change of mindset needed from both patients and providers to alter diabetes management practices is more difficult; more challenging still are the staffing and strategies for the analysis of data for each patient.

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## ODYSSEY DM Program: PCSK9 Improves Lipid Profiles in Patients With Type 2 Diabetes

Members of the ODYSSEY Diabetes Mellitus (DM) Steering Committee revealed the results of 2 trials, ODYSSEY DM-Insulin and ODYSSEY DM-Dyslipidemia, at the 77th Scientific Sessions of the American Diabetes Association (ADA). They are the first trials to evaluate alirocumab, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, a therapy to treat patients with type 2 diabetes (T2D). Alirocumab is a fully humanized monoclonal antibody to the PCSK9 protein. In patients at high risk of cardiovascular disease (CVD), it reduces circulating low-density lipoprotein cholesterol (LDL-C) by sequestering PCSK9; this action blocks PCSK9-mediated LDL receptor degradation and increases the availability of the LDL receptor to remove LDL-C from circulation, thus lowering blood cholesterol levels.<sup>1</sup>

Alirocumab has been investigated across ODYSSEY trials, in which patients with uncontrolled LDL-C achieved reductions in LDL-C to target levels ( $\leq 70$  mg/dL) that were unachievable with lipid-lowering therapy alone (maximally tolerated statins or usual care). Additionally, alirocumab treatment was associated with CVD risk reduction. Of the patients treated with alirocumab in these studies, approximately 30% ( $n = 4987$ ) had either type 1 diabetes (T1D) or T2D; however, no previous trial investigated alirocumab efficacy and safety in patients with T1D or T2D or mixed dyslipidemia.<sup>1-3</sup>

T2D is an independent risk factor for CVD. Moreover, CVD risk increases as T2D worsens, especially in patients receiving insulin.<sup>1</sup> Mixed dyslipidemia is commonly present in patients with T2D and further increases their risk of CVD. Despite the proper use of statins and other lipid-lowering therapies, many patients with T2D fail to attain desired lipid goals, resulting in unreduced risk of CV events. The ODYSSEY DM Program aimed to assess efficacy and safety of alirocumab in these high-CVD risk patients with T2D treated with insulin who also had mixed dyslipidemia, and the investigators discussed the results at the ADA 77th Scientific Sessions.<sup>1-3</sup>

### ODYSSEY DM-Insulin Trial Efficacy of Alirocumab

Lawrence Leiter, MD, MDCM, FRCPC, FACP, FACE, FAHA, director of the Lipid Clinic and associate director of the Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, presented the results from the patient cohort with T2D at high CV risk who were treated with insulin at the time of enrollment in the ODYSSEY DM-Insulin trial. The results can help guide clinical decision making, regarding these patients, beyond usual care with statin therapy, Leiter said, and provide safety information on the co-administration of a biologic (insulin) with a monoclonal antibody (alirocumab).<sup>1</sup>

Of the population enrolled, 60% had additional CV risk factors and 5% had established atherosclerotic CVD (ASCVD),

defined as coronary heart disease, peripheral arterial disease, or ischemic stroke and/or at least 1 additional risk factor of CVD. The patients had an average glycated hemoglobin (A1C) level at baseline of 7.5%, mean fasting plasma glucose of 153 mg/dL, and mean duration of T2D of 15.4 years. On average, they had used insulin for 5.6 years before randomization within the study.<sup>1</sup>

Patients with T2D were randomized 2:1 to receive either alirocumab or placebo subcutaneously every 2 weeks for 12 weeks. Patients could receive dosage increases to 150 mg at week 8, if LDL-C levels were still above target range.<sup>2</sup> All enrolled patients had not previously achieved LDL-C goals of  $< 70$  mg/dL despite maximally tolerated statin therapy with or without other lipid-lowering therapy. At baseline, lipid-lowering therapy was used for all 294 patients in the alirocumab treatment group and all 147 patients in the placebo group. About 20% to 24% of patients were statin-intolerant; rather than statins, their standard-of-care lipid-lowering therapies included, in most cases, ezetimibe and fibrates. Baseline LDL-C values were 110 mg/dL in the alirocumab arm and 145 mg/dL in the placebo arm. An independent atherosclerotic risk factor, lipoprotein a [Lp(a)], was present in 14% of patients in the alirocumab arm and 16% of the placebo arm.<sup>1</sup>

### Lipid Control

The primary end point of ODYSSEY DM-Insulin was the percent change in LDL-C from baseline to 24 weeks. Overall, alirocumab treatment significantly ( $P < .0001$ ) reduced mean LDL-C level by 49% compared with placebo treatment. The mean absolute LDL-C value decreased by 46.2% in the alirocumab arm, while there was a mean increase of 0.8% of LDL-C in the placebo arm. Significantly, 76.4% of the alirocumab-treated patients achieved target LDL-C of less than 70 mg/dL. Alirocumab demonstrated its effect on reducing LDL-C at the 8-week mark, with near-maximal reduction and additional lowering occurring after week 12 (20% of patients had their alirocumab dosage increased to 150 mg at the 12-week mark).<sup>1</sup>

From baseline to week 24, alirocumab demonstrated effect on secondary lipid parameters: there were significant reductions ( $P < .001$  for all) in non-high-density lipoprotein cholesterol (non-HDL-C) ( $-38.7\%$ ), apolipoprotein B (ApoB) ( $-36.7\%$ ), Lp(a) ( $-18.4\%$ ), and the number of LDL particles ( $-40.2\%$ ). Alirocumab also increased HDL-C ( $P = .01$ ) and reduced triglycerides ( $P = .09$ ) compared with placebo.<sup>1</sup>

### Diabetes Control

Importantly, alirocumab did not impact the key diabetes-related end points, including change from baseline in glucose homeostasis measured by A1C and fasting plasma glucose, total daily insulin dose, and the number of glucose-lowering agents used.

In this analysis of glycemia-related key secondary outcomes, alirocumab did not reveal changes to A1C fasting or plasma glucose observed over the 24-week trial and was similar to placebo. Additionally, the results of the Insulin trial revealed no changes in median insulin dose or number of antihyperglycemic agents added to treatment to control diabetes.<sup>1</sup>

The safety analysis demonstrated that although there was no difference in treatment-related adverse events (TRAEs), the incidence of serious AEs was lower in the alirocumab treatment group than placebo (7.5% vs 9.7%, respectively). Over the 24-week study period, there were more discontinuations of study treatment in the alirocumab group compared with placebo (5.1% vs 1.4%, respectively). TRAEs were similar in both groups and included nasopharyngitis, myalgia, arthralgia, and cough. Myalgia occurred in 4.4% of alirocumab-treated patients compared with 0.7% of the placebo group and arthralgia in 1.7% of alirocumab-treated patients and 2.8% in placebo.<sup>1</sup>

### ODYSSEY DM-Dyslipidemia

Robert Henry, MD, professor of medicine in the Division of Endocrinology and Metabolism, Department of Medicine, University of California San Diego School of Medicine, and director of the Center for Metabolic Research for San Diego's Veterans Affairs Healthcare System, presented the results from the 24-week treatment period at the ADA 77th Scientific Sessions. ODYSSEY DM-Dyslipidemia was the first dedicated phase 3b/4 trial investigating the efficacy and safety of alirocumab in a head-to-head comparison with standard lipid-lowering therapy in patients with T2D and mixed dyslipidemia who are at a high risk of CV events because of uncontrolled non-HDL-C despite maximally tolerated statin therapy.<sup>1</sup>

A total of 413 patients were randomized 2:1 to receive alirocumab (n = 273) or usual care (n = 136) for the 24-week study period. In the alirocumab group, the drug was administered subcutaneously with a starting dose of 75 mg every 2 weeks for 24 weeks, with a blinded dose increase to 150 mg at week 12 if patients had non-HDL-C  $\geq 100$  mg/dL at week 8. Patients were well matched for baseline characteristics, including duration of diabetes (approximately 11 years). One-third of the treatment group had ASCVD, defined as coronary heart disease, pulmonary arterial disease, or a history of ischemic stroke with at least 1 additional CV risk factor. Sixty-five percent of the population had CV risk.<sup>1</sup>

Mixed dyslipidemia was defined as uncontrolled non-HDL-C of  $\geq 100$  mg/dL and triglycerides of  $\geq 150$  mg/dL and  $< 500$  mg/dL, despite treatment with stable maximally tolerated statin therapy.<sup>1,3</sup> Usual care included lipid-lowering therapies; high-intensity statins were used in 46.3% of alirocumab-treated patients and 36.2% of usual-care patients, and 18% of patients from both groups were statin-intolerant.<sup>3</sup> Antihyperglycemic agents (AHAs) were used in 15.6% and 22.6% of the alirocumab and usual-care groups, respectively. The majority of AHA usage was attributed

“ Alirocumab was shown to be an effective treatment in the reduction of cholesterol and lipids compared with standard care. ”

to metformin (76%), while sulfonylurea treatment was used in 24.4% of the alirocumab and 22.6% in the usual-care group.<sup>1</sup>

### Lipid Control

In the first trial of the ODYSSEY program to set the primary efficacy end point as the percent change in non-HDL-C, alirocumab demonstrated significant effect: non-HDL-C decreased by a mean of 32.5% from baseline to week 24 compared with usual care ( $P < .0001$ ).<sup>1,3</sup> Absolute change from baseline to week 24 was a reduction of 37.3% with alirocumab compared with 4.7% with usual care. The alirocumab patient group had significant reductions in non-HDL-cholesterol at 8 weeks, with persistent reductions overtime, and additional decrease at 20 weeks. The alirocumab dose was increased at week 12 in 36.4% of the test population (63.6% maintained at 75 mg). Ultimately, in the alirocumab group, significantly ( $P < .0001$ ) more patients achieved non-HDL-C targets of less than 100 mg/dL compared with usual care (66.9% vs 17.7%).<sup>1</sup>

A significantly ( $P < .0001$ ) greater proportion of patients treated with alirocumab achieved target LDL-C of less than 70%: 70.8% versus 16.3% in the alirocumab and usual-care groups, respectively.<sup>1</sup> Alirocumab treatment also demonstrated significant ( $P < .0001$ ) improvements from baseline to 24 weeks in the key secondary end points of lipid parameters in the treated population compared with usual care: these were in LDL-C (-43.0%), ApoB (-32.3%), total cholesterol (-24.6%), Lp(a) (-27.5%), and LDL particle number reduction of 37.8%.<sup>1,3</sup>

### Diabetes Control

Diabetes-specific end points including absolute change from baseline in A1C, fasting plasma glucose, and number of glucose-lowering agents were evaluated.<sup>3</sup> As in the ODYSSEY DM-Insulin cohort, alirocumab did not significantly affect any of these over the 24 weeks of evaluation.<sup>1</sup>

The safety and tolerability of alirocumab were evaluated by several end points, including TRAEs and laboratory data including microalbuminuria.<sup>3</sup> TRAEs were well balanced between the cohorts with incidences of 67.3% with alirocumab and 66.5% with standard care. Serious TRAEs occurred at a higher incidence in the alirocumab group (6.9% vs 5.1%); the most frequent TRAEs were urinary tract infections, diarrhea, and nasopharyngitis.<sup>1</sup>

### Conclusion

Alirocumab was shown to be an effective treatment in the reduction of cholesterol and lipids. “We studied 2 groups of

very high-risk people with diabetes mellitus—those on insulin and those with mixed dyslipidemia for whom, previously, only secondary data were available,” stated Henry. “These studies demonstrated the superior lipid-lowering efficacy of alirocumab compared with standard care, with no new safety issues.” Additional results will be presented on the efficacy of alirocumab compared with that of fenofibrates; also forthcoming will be a detailed analysis to better understand the mechanism of action of alirocumab on atherogenic mixed dyslipidemia.<sup>1</sup> ●

### Prediction of Readmission Risk (Continued from page 16)

Scientific Sessions that identified predictive risk factors and offered actionable insights to improve diabetes inpatient and outpatient care to reduce unnecessary hospitalizations. ●

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### Remote Monitoring of A1C in Type 1 Diabetes (Continued from page 27)

For a strategy like this to be adopted universally, providers will need to change the standard workflow and payers will need to alter reimbursement. “We [would be] asking providers to completely change the way they deliver care,” said Vojta. “Instead of retrospective analysis occurring quarterly, we [would] need daily evaluation of patient data.”<sup>1</sup>

Another roadblock for daily glucose-monitoring data analysis is the absence of a universal software platform to evaluate data across different devices and pumps. In the Minnesota study, patients utilized proprietary software platforms. Vojta added, “We now have the opportunity to [shift] our current practice model from expensive, ineffective care based on quarterly visits

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for patients... [to] automated, less expensive, patient-centered technology. This new intervention needs to be disciplined and focused on what we do as caregivers. However, adoption of this system will need patients and physicians to engage in learning new technology and to conduct studies of economic and clinical outcomes in order to convince payers of intervention benefits and incorporation into practice guidelines.”<sup>1</sup> ●

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