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THE PRESENT AND FUTURE: *JACC* STATE-OF-THE-ART REVIEW

The Changing Landscape of Diabetes Therapy for Cardiovascular Risk Reduction

JACC State-of-the-Art Review

Jonathan D. Newman, MD, MPH,[a] Anish K. Vani, MD,[a] Jose O. Aleman, MD, PhD,[b] Howard S. Weintraub, MD,[a] Jeffrey S. Berger, MD, MS,[a] Arthur Z. Schwartzbard, MD[a]

ABSTRACT

Type 2 diabetes mellitus (T2D) is a major risk factor for cardiovascular disease (CVD), the most common cause of death in T2D. Despite improved risk factor control, however, adults with T2D continue to experience substantial excess CVD risk. Until recently, however, improved glycemic control has not been associated with robust macrovascular benefit. The advent of 2 new classes of antihyperglycemic agents, the sodium-glucose cotransporter-2 inhibitors and the glucagon-like peptide-1 receptor agonists, and their respective large cardiovascular outcome trials, has led to a paradigm shift in how cardiologists and heath care practitioners conceptualize T2D treatment. Herein, the authors review the recent trial evidence, the potential mechanisms of action of the sodium-glucose cotransporter-2 inhibitors and the glucagon-like peptide-1 receptor agonists, safety concerns, and their use for the primary prevention of CVD as well as in diabetic patients with impaired renal function and heart failure. (J Am Coll Cardiol 2018;72:1856–69)

Type 2 diabetes mellitus (T2D) is a major risk factor for cardiovascular disease (CVD), the most common cause of death in T2D (1). Traditional CVD risk factor management for patients with T2D who have or are at elevated risk for CVD includes a multifactorial lifestyle intervention along with intensive interventions to control blood pressure, lipids, antiplatelet therapy, and glycemic therapy, as reviewed previously (2). A focus on traditional risk factor control has led to substantial reductions in the burden of CVD for adults with T2D (3,4). Despite improved risk factor control, however, adults with T2D continue to experience substantial excess CVD risk. Historically, many physicians have dichotomized management of patients with diabetes into 2 categories: 1) improve glycemic control to reduce microvascular complications; and 2) control established CVD risk factors, such as tobacco use, hyperlipidemia, and hypertension to reduce the risk of macrovascular disease, the biggest driver of

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From the [a]Division of Cardiology and Center for the Prevention of Cardiovascular Disease, Department of Medicine, New York University Medical Center, New York, New York; and the [b]Division of Endocrinology, New York University Medical Center, New York, New York. Drs. Newman and Berger have been partially funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health (K23HL125991 to Dr. Newman; HL114978 to Dr. Berger). Dr. Aleman has been partially funded by the American Heart Association. Funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the paper. Dr. Weintraub has received honoraria from Amgen, Sanofi, and Gilead for consulting; has served on the Speakers Bureau for Amgen; and has received research funding from Amarin, Sanofi, Akcea, and Ionis. Dr. Berger has received research funding from AstraZeneca and Janssen. Dr. Schwartzbard has received research funding to New York University from Merck/Pfizer, Amarin, Sanofi, and Ionis; and has served as a consultant to the formulary committee for Optum Rx. Dr. Vani has reported that he has no relationships relevant to the contents of this paper to disclose.

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morbidity and mortality for patients with T2D. In this setting, antidiabetic agents were used primarily for glucose lowering, requiring titration and monitoring of therapy even though glycemic control had not been associated with reduced cardiovascular (CV) risk. Cardiologists and other providers caring for the diabetic patient deferred diabetes management to experts in endocrinology or diabetes care. Over the last several years, trials designed first to demonstrate safety of newer antidiabetic agents demonstrated superiority for CVD risk reduction among adults with T2D with a history of or at high risk for recurrent CVD events. These findings have implications for cardiologists and health care providers who commonly care for adults with T2D and elevated CVD risk.

Herein, we will review and integrate these recent data into updated management pathways for adults with T2D who are at high risk for CVD. The focus will be upon reviewing recent trial evidence for agents in the 2 major new classes with demonstrated efficacy for CVD risk reduction: the sodium-glucose cotransporter 2 inhibitors (SGLT2-i) and the glucagon-like peptide-1 receptor agonists (GLP-1 RA). Recent reviews have included most (5-7), but not all (8,9) recent CV outcome trials with relevance for care of adults with T2D and heightened CVD risk. We will add to recent reviews by including an examination of the use of SGLT2-i and GLP-1 RA for cardiorenal protection in the high-risk diabetic patient, and also focus on the use of these agents in the setting of comorbid heart failure (HF) risk. We will also examine the role of background CV and antidiabetic medical therapy in these recent trials. Finally, we will examine emerging evidence for use of these agents for primary as well as secondary CVD prevention. A discussion of other agents, such as dipeptidyl peptidase-4 inhibitors, with less well-established CVD risk reduction profiles is beyond the scope of this review, and we refer the interested reader to prior reviews for an examination of other antidiabetic drug classes for CVD risk reduction in the high-risk adult with T2D (10,11).

THE DEVELOPMENT OF CV SAFETY AND OUTCOME TRIALS FOR THE HIGH-RISK DIABETIC PATIENT

The rationale for the development of CV outcome studies has been reviewed in detail previously (11,12). In brief, partly due to signals of adverse CV safety with earlier glucose-lowering medications (13), the U.S. Food and Drug Administration (FDA) and European Medicines Agency subsequently required new glucose-lowering therapies to demonstrate CV safety in prospective, randomized controlled outcome trials (12). Designed for detection of risk signals, some of these CV outcome trials have not only demonstrated CV safety, but have also shown robust reductions in CV events and all-cause mortality (5-8). As recommended (12), these CV outcome trials have focused primarily on high-risk diabetic patients, such as patients with pre-existing vascular disease, renal impairment, advanced age, or multiple risk factors for CVD. These patients are commonly referred to cardiology practices, and an in-depth review of the results from recent major CV outcome trials will assist the cardiologist and other health care practitioners in caring for the high-risk patient with T2D. We will begin by reviewing the mechanism and major trial outcomes and safety for the SGLT2-i, followed by a discussion of the GLP-1 RA. We will then discuss issues germane to both classes of agents in recent CV outcomes trials, including issues related to concomitant CV medical therapy and insulin use in these recent CV outcomes trials, and the application of these newer agents for the primary prevention of CVD in adults with T2D. A summary of the major trial results is presented in **Table 1**.

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease
GLP-1 RA = glucagon-like peptide-1 receptor agonists
HbA_{1c} = glycated hemoglobin
HR = hazard ratio
LDL = low-density lipoprotein
MI = myocardial infarction
SGLT2-i = sodium-glucose cotransporter-2 inhibitors
T2D = type 2 diabetes mellitus

THE SGLT2 INHIBITORS

The SGLT2-i have demonstrated impressive reductions in CV risk in 2 major CV outcomes trials, EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and the CANVAS Program (Canagliflozin Cardiovascular Assessment Study) (5,8), with other trials in this drug class ongoing (14). The potential mechanisms of effect have been described in detail (15), and will be summarized here and in the **Central Illustration**.

POTENTIAL MECHANISMS OF BENEFIT FOR THE SGLT2 INHIBITORS. Metabolic effects. SGLT2-i work by inhibiting the high-capacity, low-affinity SGLT2 receptor in the proximal tubule of the kidney, which is responsible for reabsorbing approximately 90% of filtered glucose (16). Paradoxically, in hyperglycemic states such as diabetes, SGLT2 activity is increased and leads to greater reabsorption of both glucose and salt (17). Importantly, for safety, the glucose-lowering effects of SGLT2-i decrease at lower plasma glucose levels, thereby accounting for the reduced risk of hypoglycemia seen with this class of antidiabetic agents (15). As seen in EMPA-REG OUTCOME and the CANVAS Program, treatment with SGLT2-i improves CV and microvascular endpoints in patients with T2D (5,8). Notably, the difference in magnitude reduction in glycated hemoglobin (HbA_{1c})

TABLE 1 Summary of the GLP-1 RA and SGLT2-i Cardiovascular Outcome Trials

	EMPA-REG	CANVAS	LEADER	SUSTAIN-6
Agent	Empagliflozin	Canagliflozin	Liraglutide	Semaglutide
n	7,020	10,142	9,340	3,297
Median follow-up, yrs	3.1	2.4	3.8	2.1
Mean baseline HbA_{1c}, %	8.1	8.2	8.7	8.7
Primary outcome	**CV death** Nonfatal MI Nonfatal stroke	CV death Nonfatal MI Nonfatal stroke	**CV death** Nonfatal MI Nonfatal stroke	CV death Nonfatal MI **Nonfatal stroke**
HR (95% CI)	**0.86** (0.74–0.99), p = 0.04	**0.86** (0.75–0.97), p = 0.02	**0.87** (0.78–0.97) p = 0.01	**0.74** (0.58–0.95) p = 0.02
Adverse events	Genital infections (male and female)	Amputations, fractures, male genital infections, female mycotic infections, volume depletion	Acute gallstone disease, injection site reactions, and adverse events leading to drug discontinuation (nausea, vomiting, diarrhea, abdominal pain/discomfort, anorexia)	Retinopathy, gastrointestinal disorders, any adverse leading to drug discontinuation (nausea, vomiting, diarrhea in a dose-dependent response)

Bolded outcome was statistically significant ($p < 0.05$).

GLP-1 RA = glucagon-like peptide-1 receptor agonists; HbA_{1c} = hemoglobin A1c; HR = hazard ratio; SGTL2-i = sodium-glucose cotransporter 2 inhibitors.

between the active treatment and placebo arms in these trials was modest (0.3% and 0.6% in EMPA-REG OUTCOME and CANVAS, respectively) and is unlikely to account for the reduction in CV events with SGLT2-i (5,8). Although still speculative, the nonglycemic effects of SGLT2-i likely drive the observed weight loss, reduction in blood pressure, and preservation of renal function. Improvements in these pathogenic risk factors may reduce CV events, heart failure, and progression of nephropathy (15). Interestingly, both empagliflozin and canagliflozin demonstrated small increases (≈3 to 4 mg/dl increases in low-density lipoprotein [LDL] cholesterol) over the trial duration (5,8,18). Some SGLT2-I, such as canagliflozin, have also been shown to reduce epicardial adipose tissue, which may be linked to coronary atherogenesis and impaired myocardial function, possibly providing an additional mechanism of CV benefit for SGLT2-i (19); a clinical trial examining dapagliflozin and epicardial adipose tissue is ongoing (NCT02235298).

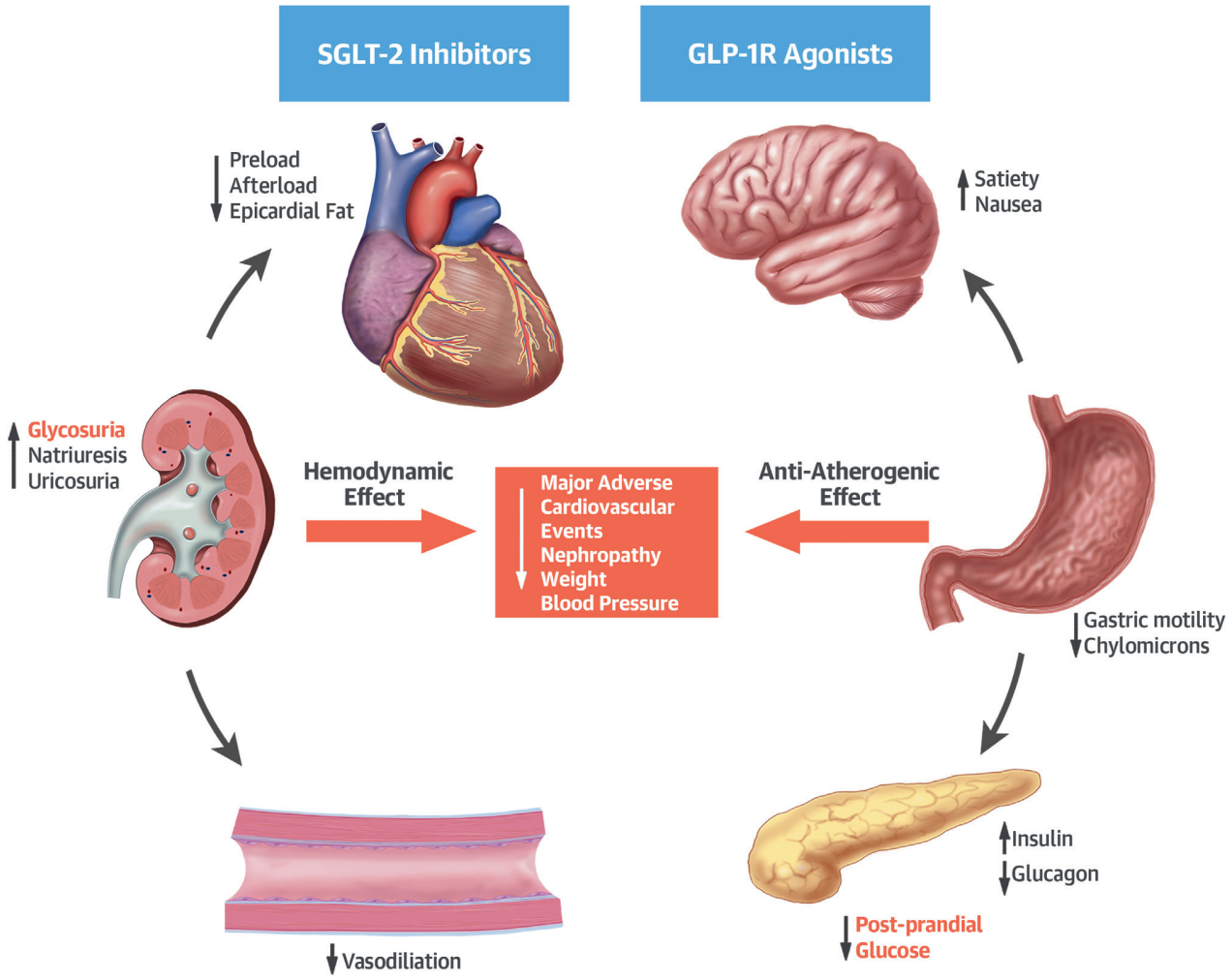
SGLT2-i-induced glucosuria can promote uric acid excretion, with animal models suggesting a possible inhibitory effect of glucosuria on uric acid reabsorption mediated by the GLUT9 isoform 2 transporter (20). High uric acid levels have been associated with increased CV and renal disease (21). Glucosuria also leads to ongoing caloric loss, a persistent catabolic state, and increased ketogenesis (15). The resulting mild ketonemia caused by SGLT2-i may be an efficient fuel substrate for the heart, and may mitigate some of the metabolic effects associated with incipient heart failure (18).

Hemodynamic effects. The very early reduction in CV mortality observed in the EMPA-REG OUTCOME

along with heterogeneity of the hazard ratios (HRs) for the atherosclerotic components of the 3-point major adverse cardiovascular events (MACE-3), suggest that the early cardioprotective mechanism of benefit from SGLT2-i may be related to improved hemodynamic status (5,8,22). This reasoning is supported by a recent post hoc mediation analysis of EMPA-REG OUTCOME, which demonstrated that plasma volume, as measured by hemodynamic markers (e.g., hematocrit), appeared to have a larger effect on the reduction of CV mortality than measures of glycemia (23).

SGLT2-i may also derive hemodynamic benefit through a reduction in blood pressure, but this is unlikely to explain the rapid reduction in CV mortality observed in the SGLT2-i CV outcome trials. A meta-analysis of 27 SGLT2-i trials demonstrated a systolic blood pressure reduction of approximately 4 mm Hg among patients with T2D, likely driven by natriuresis osmotic diuretic effects (24). Animal studies have suggested that SGLT2-i have the potential to restore nocturnal dipping and have an additive effect when combined with use of a renin-angiotensin-aldosterone system inhibitor, possibly due to effects of the renin-angiotensin-aldosterone system in the volume-contracted state (15,25). The natriuretic and diuretic effects of SGLT2-i may also improve arterial stiffness (15), an independent subclinical predictor of CV risk and mortality (26), although the exact mechanism remains unclear. Moreover, a reduction in blood pressure can mitigate heart failure risk by reducing cardiac afterload and improving coronary flow and cardiac contractility. A reduction in plasma volume via natriuresis and os-

CENTRAL ILLUSTRATION **Potential Pathways of Cardiovascular Benefit From Use of SGLT2 Inhibitors and GLP-1 Receptor Antagonists for Patients With T2D**



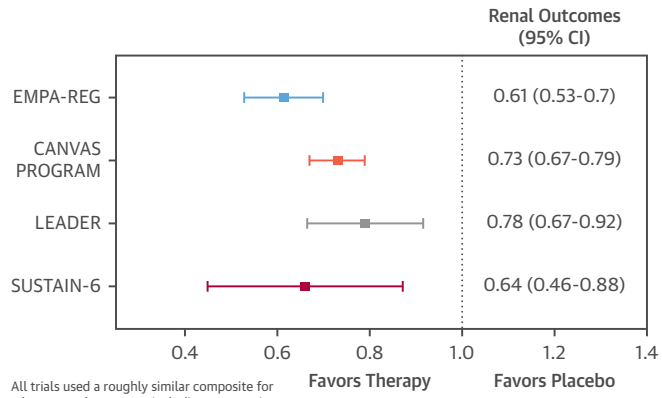
Newman, J.D. et al. J Am Coll Cardiol. 2018;72(15):1856–69.

Potential mechanisms of action of sodium-glucose cotransporter 2 (SGTL2) inhibitors and glucagon-like peptide receptor (GLP-1 R) agonists to mediate glycemic control and cardiovascular benefit. The cardiovascular benefit of SGLT2 inhibitors may occur through glycosuria and favorable hemodynamic effects. Conversely, the benefit of the GLP-1 R agonists may occur via post-prandial pancreatic insulin secretion and favorable antiatherogenic effects.

myocardial stretch, thus protecting against the progression of heart failure and arrhythmogenesis, respectively (27).

The effects of SGLT2-i on renal hemodynamics and glomerular function may be a primary mechanism through which CV benefit from this class of agents is derived. The cardiorenal benefits of SGLT2-i include lowering intraglomerular pressure and reducing diabetic hyperfiltration (28), a process characterized by diminished distal salt delivery and maladaptive arteriole vasodilatation and hyperfiltration (29). SGLT2-i counteract this process and lower intraglomerular pressure leading to cardiorenal protective effects for patients with diabetes. A reduction in intraglomerular pressure may also suppress renal inflammation and fibrosis, further protecting against nephropathy and albuminuria (15). Current evidence from CV outcome trials with SGLT2-i supports this possibility (**Figure 1**). The ongoing CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and

FIGURE 1 Summary of Renal Benefits in Major Recent Trials of SGTL2-i and GLP-1 RA



Renal outcomes were all favorably reduced by therapy in EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS PROGRAM (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes). All trials used a roughly similar composite for adverse renal outcomes including progression of albuminuria. CI = confidence interval; SGLT2-i = sodium-glucose co-transporter 2 inhibitor.

Diabetic Nephropathy) trial (NCT02065791) evaluating primary renal endpoints will further define the cardiorenal protective effects of canagliflozin in approximately 4,200 adults with T2D and diabetic nephropathy (defined as stage 2 or 3 chronic kidney disease with macroalbuminuria) on a maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (30). The primary endpoint of this important trial includes a composite of end-stage renal disease, doubling of serum creatinine, and renal or CV death.

CLINICAL TRIAL EVIDENCE SUPPORTING SGLT2-I USE FOR THE REDUCTION OF CVD. Major CV outcome trials have been completed for 2 agents in this class: empagliflozin (EMPA-REG OUTCOME) and canagliflozin (CANVAS Program) (5,8), with results from trials of other agents expected in 2019 (15,30,31). In both EMPA-REG OUTCOME and the CANVAS Program, SGLT2-i led to reductions in MACE-3 (CV death, nonfatal myocardial infarction [MI]; or nonfatal stroke) (**Figure 2**). Reduced heart failure hospitalizations (**Figure 2**) and renal outcomes (**Figure 1**) were also demonstrated, but were not formally tested in the CANVAS Program because of the hierarchical testing plan (8). One difference between EMPA-REG OUTCOME and the CANVAS Program is the signifi-

empagliflozin, both of which were not observed in the CANVAS Program (5,8).

The main reason for the difference in study outcomes between these 2 trials may be attributable to differences in the enrolled study populations and differential follow-up duration. Participants in EMPA-REG OUTCOME were followed for a median of 3.1 years and all were required to have a history of CV disease (coronary artery disease, stroke, or peripheral artery disease). Participants in the CANVAS Program were followed for a shorter duration (median of 2.4 years) and could have either CV risk factors alone (34% of participants) or established CVD (66%). Reflecting the higher-risk population enrolled in EMPA-REG OUTCOME (secondary prevention), the MACE-3 composite and all-cause mortality were substantially higher in placebo group of EMPA-REG OUTCOME compared with the CANVAS Program (43.9 per 1,000 patient-years vs. 31.5 per 1,000 patient-years, respectively) (5,8,14). The CANVAS Program is a combination of 2 separate studies; although both had identical entry criteria (8), follow-up duration differed substantially: mean follow-up duration in CANVAS was 5.7 years, versus 2.1 years in the CANVAS-R study (8). As noted previously (14), the combination of ≈ one-third primary prevention patients in the CANVAS program and shorter-term treatment in roughly one-half of the population (CANVAS-R) may partially explain a smaller effect of canagliflozin compared with empagliflozin.

Cardiorenal protection and SGLT2-i. Type 2 diabetes is a major risk factor for macrovascular and microvascular disease (32). Kidney disease develops in nearly 35% of patients with T2D and is associated with increased mortality (33). Both EMPA-REG OUTCOME and the CANVAS Program demonstrated cardiorenal protective effects of SGLT2-i with empagliflozin or canagliflozin, respectively (**Figure 1**). The renal benefits of empagliflozin were reported as a pre-specified secondary analysis from EMPA-REG OUTCOME (34). Participants in EMPA-REG OUTCOME had an estimated glomerular filtration rate ≥30 ml/min per 1.73 m^2 of body surface area (5). The pre-specified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria (34). Overall, there was nearly a 40% reduction (HR: 0.61; 95% confidence interval [CI]: 0.53 to 0.70) in the primary renal outcome (absolute risk reduction 6.1%) for participants receiving empagliflozin compared with placebo (**Figure 1**) (34). Although the CANVAS Pro-

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