

MINI FOCUS ON DIABETES

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

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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 health 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) © 2018 by the American College of Cardiology Foundation.

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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Exhibit #

Exhibit 2602

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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.

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})

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

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; SGLT2-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).

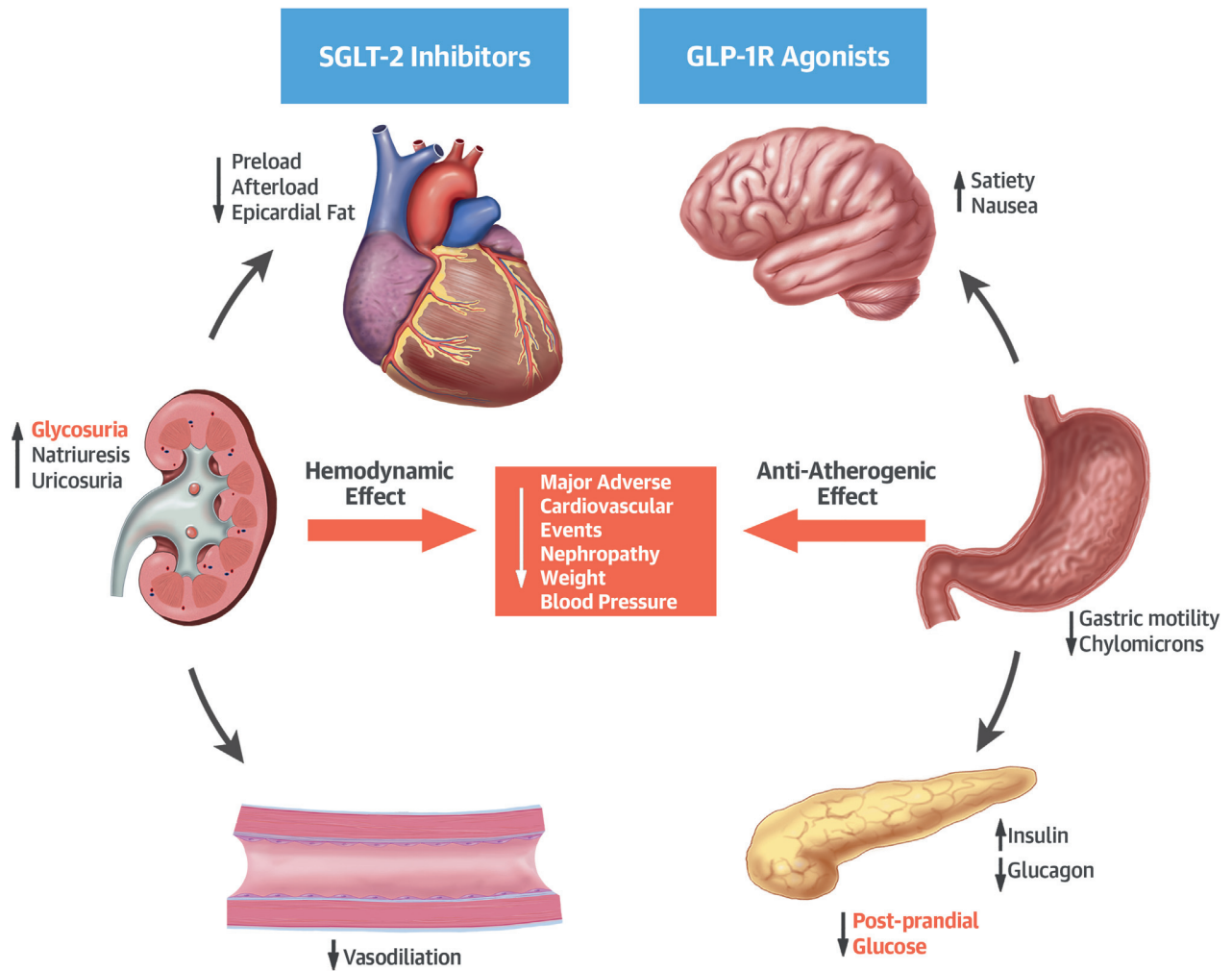
SGLT2-i-induced glucosuria can promote uric acid excretion, with animal models suggesting a possible inhibitory effect of glucosuria on uric acid reabsorption mediated by the GLUT9 isoform 2 transporter (20). High uric acid levels have been associated with increased CV and renal disease (21). Glucosuria 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 trial and early reduction in heart failure in CANVAS,

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 sub-clinical 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 osmotic diuresis can also reduce cardiac pre-load and

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



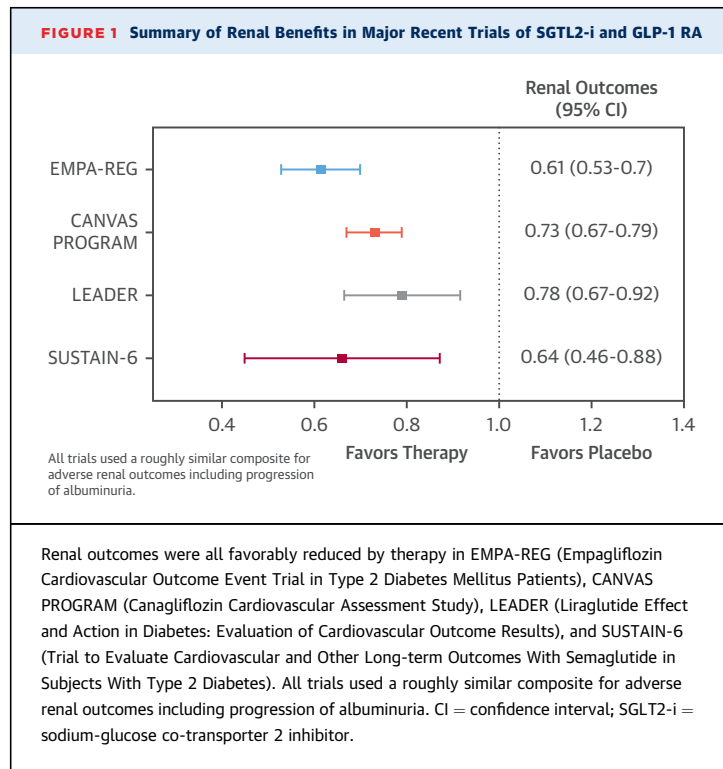
Newman, J.D. et al. J Am Coll Cardiol. 2018;72(15):1856-69.

Potential mechanisms of action of sodium-glucose cotransporter 2 (SGLT2) 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 tubuloglomerular feedback, resulting in afferent

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 Cardiovascular Outcomes in Participants With



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 significant reduction in CV and all-cause mortality with

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

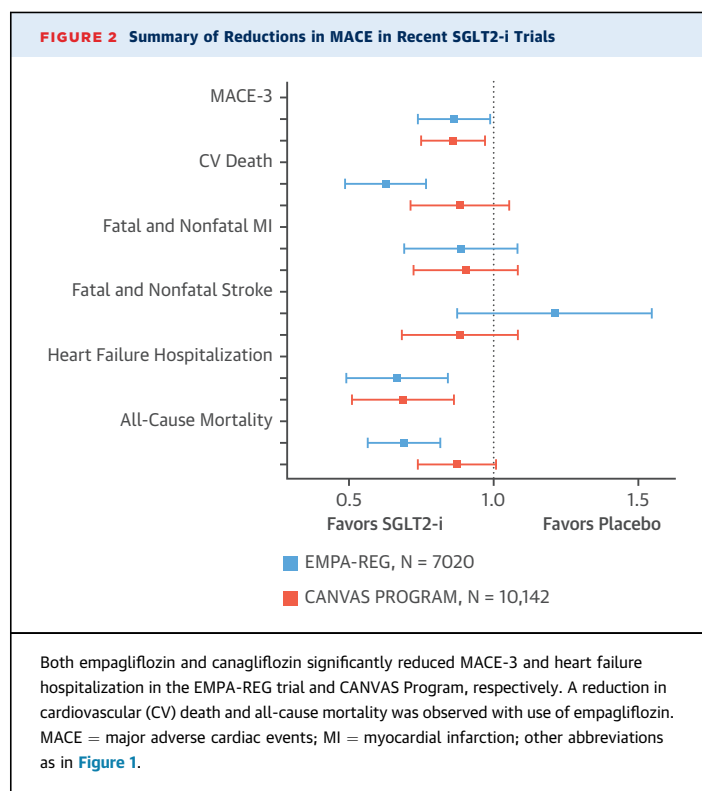
The main reason for the difference in study outcomes between these 2 trials may be attributable to differences in the enrolled study populations and differential follow-up duration. Participants in EMPA-REG OUTCOME were followed for a median of 3.1 years and all were required to have a history of CV 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 m² 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 Program analysis plan precluded formal assessments of

statistical significance, the point estimates for reduction in renal events with empagliflozin and canagliflozin suggest a consistency of benefit for reduction in renal events with SGLT2-i (5,8). A post hoc analysis of the CANVAS Program evaluating participants with an estimated glomerular filtration rate (eGFR) down to 30 ml/min/1.73 m² found a similar reduction in CV events and progression of kidney disease among those with impaired renal function at baseline, despite a progressive attenuation of HbA_{1c} lowering with SGLT2-i at lower eGFR (35).

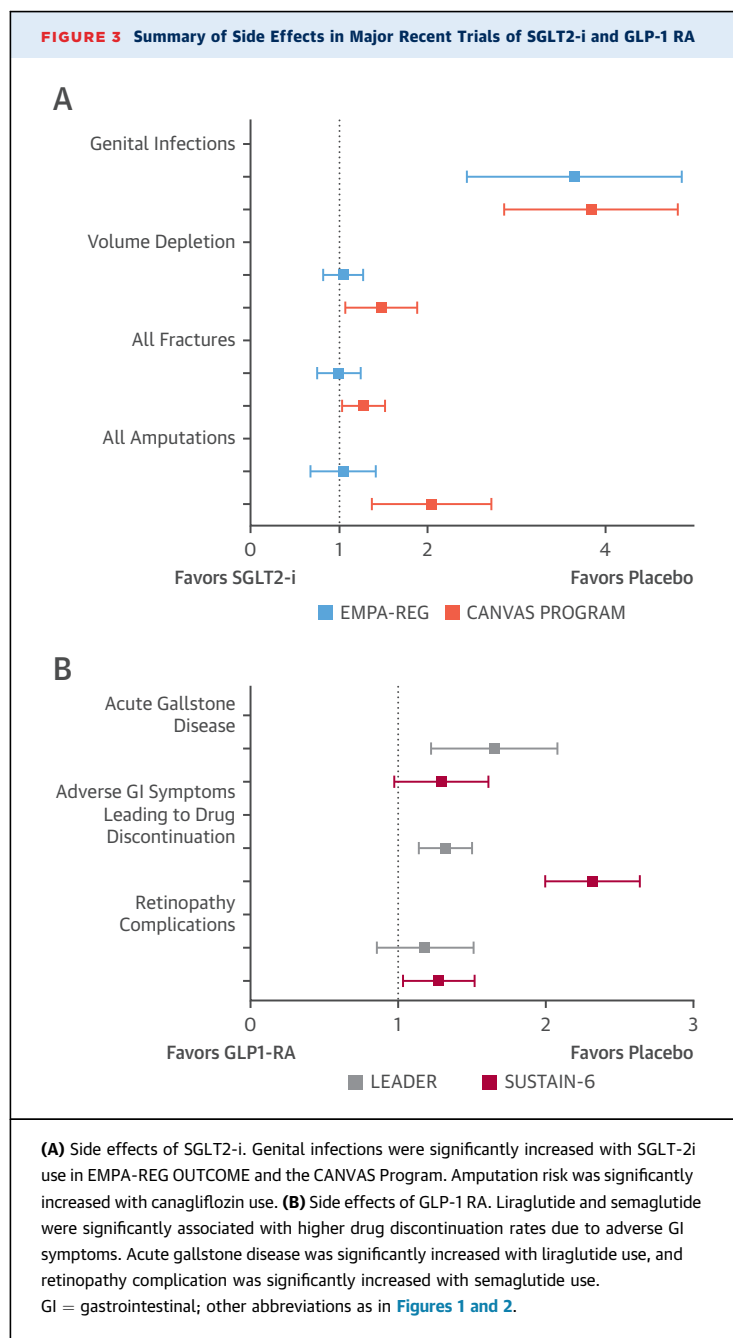
Heart failure benefits and SGLT2-i. Similar to the relationship between diabetes and renal dysfunction, heart failure (HF) is also highly prevalent in patients with T2D (36). Patients with T2D and comorbid HF have an extremely poor prognosis, with a median survival of approximately 4 years (37). As shown in Figure 2, the magnitude of reduction in the heart failure composite endpoint is similar for empagliflozin and canagliflozin (22,38). It has been suggested that the rapid benefit observed with SGLT2-i is unlikely due to reductions in atherothrombotic events via improved control of classical CV risk factors, but rather related to the hemodynamic and diuretic effects of SGLT2-i given the rapidity of benefit (38-40). Limitations of these trials include the absence of systematically collected baseline biomarkers of heart failure or echocardiography data (22,38). It is also important to note that EMPA-REG OUTCOME and the CANVAS Program were not designed as heart failure trials and had few patients with investigator-reported heart failure at baseline. Moreover, the safety and efficacy of SGLT2-i in patients with clinical symptoms of heart failure is unknown. However, given the baseline characteristics of patients included in these studies (older, long duration of T2D, comorbid CAD and hypertension), and the high usage of drugs to treat heart failure, it is reasonable to assume that the burden of comorbid left ventricular dysfunction and/or HF in this population was substantial (22). Recent analyses have also suggested the reduction in HF and mortality may be a class effect applicable to a broad population of patients with T2D in real-world practice settings (41,42). The ongoing heart failure trials with empagliflozin (EMPEROR-HF [EMPagliflozin outcome tRial in patients with chrOnic heaRt failure]) and dapagliflozin (DAPA-HF [Dapagliflozin-Heart Failure]) will provide further insight into SGLT2-i and heart failure in patients with and without diabetes, as well as heart failure patients with both preserved and reduced ejection fraction.

REPORTED SIDE EFFECTS OF SGLT2-I USE IN CV OUTCOME TRIALS. Figure 3A presents the a summary of the side effects observed in the major SGLT2-i CV



outcome trials (5,8). In general, empagliflozin and canagliflozin were well tolerated. Approximately 23% and 29% of participants in EMPA-REG OUTCOME and CANVAS discontinued active study drug, compared with 29% and 30% for placebo, respectively (5,8). The percent discontinuation of active drug is similar to other major placebo-controlled CV outcome trials (43). Genital infections were more common with SGLT2-i versus placebo in both EMPA-REG OUTCOME and the CANVAS Program. However, these infections infrequently resulted in study drug discontinuation. Additionally, there were differences in the definition and sex distribution of genital infections between the 2 trials, but these differences also did not appear to influence rates of drug discontinuation (5,8). Importantly, there was no difference in the occurrence of complicated urinary tract infections between participants receiving SGLT2-i compared with placebo in these trials. The risk of volume depletion appears similar with both empagliflozin and canagliflozin, though volume depletion was statistically more common only in the CANVAS Program (5,8). The CANVAS Program identified new safety concerns for amputations and fractures, which were collected as an adverse event of special interest (Figure 3A). Increased risk of fractures or amputations have not

FIGURE 3 Summary of Side Effects in Major Recent Trials of SGLT2-i and GLP-1 RA



been demonstrated with empagliflozin (44,45), although lower limb amputations were not pre-specified events of concern in EMPA-REG OUTCOME. Although increased amputations with canagliflozin have also been reported from the FDA's Adverse Event Reporting System (46) and in a propensity-matched cohort from the U.S. Department of Defense Military Health System (42), a plausible mechanism for effects of SGLT2-i on bone or vascular biology has not been determined (14).

THE GLP-1 RECEPTOR AGONISTS

In comparison to the CV outcomes trials with SGLT2-i, trial results with the GLP-1 RA have been more heterogeneous (6,7,9,47); there are additional trials ongoing using albiglutide (HARMONY outcomes [Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus]; NCT02465515) and dulaglutide (REWIND [Researching Cardiovascular Events With a Weekly Incretin in Diabetes]; NCT01394952). The potential mechanisms of effect have been described in detail (48,49), and are summarized here and in the Central Illustration.

POTENTIAL MECHANISMS OF BENEFIT FOR THE GLP-1 RECEPTOR AGONISTS. Oral glucose ingestion results in higher serum insulin levels than an equivalent parenteral glucose load, likely mediated by the incretin pathway (50). Glucagon-like peptide (GLP)-1, a type of incretin polypeptide, is secreted by the distal intestinal L-cells in response to oral nutrient ingestion and has several downstream effects prior to its rapid degradation by DPP4. (51). Endogenous GLP-1 acts primarily to stimulate pancreatic beta cells to release insulin and inhibit glucagon secretion, thereby providing a glucose-dependent mechanism to reduce post-prandial hyperglycemia without resulting in significant hypoglycemia (52). In vivo and animal studies have demonstrated a GLP-1-mediated increase in pancreatic islet and beta-cell mass, highlighting a potential mechanism to retard T2D progression (53). The incretin pathway may be impaired in T2D secondary to reduced GLP-1 secretion and resistance, providing a target for pharmacological intervention (54).

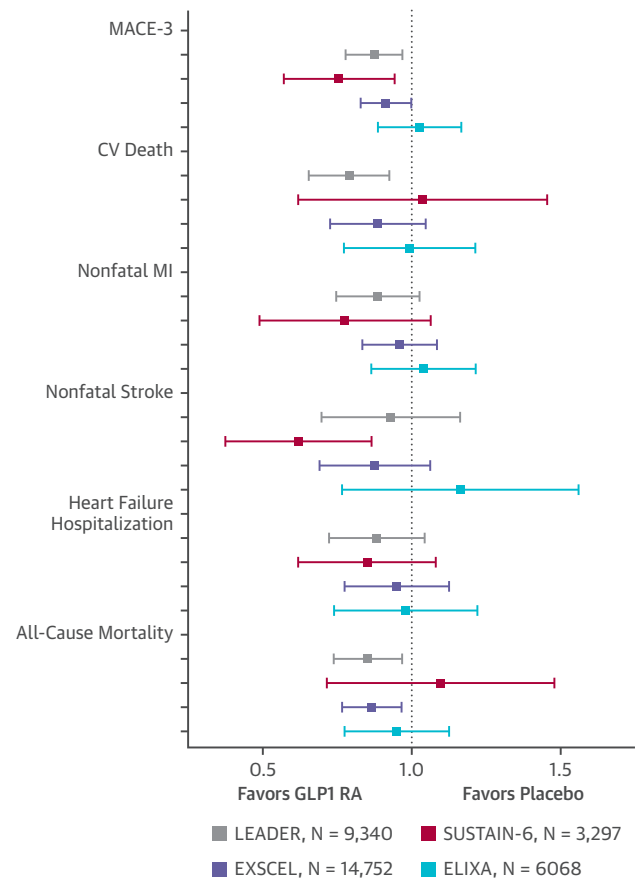
Synthetic GLP-1 RA are resistant to DPP4 degradation and accentuate the pleiotropic effects associated with GLP-1 polypeptides (55). To date, there are 6 FDA-approved GLP-1-RA, which differ in structure and duration of effect. These include: exenatide (both short- and long-acting formulations), liraglutide, semaglutide, dulaglutide, lixisenatide, and albiglutide. Both exenatide and lixisenatide are derived from exogenous Gila monster venom, whereas the others are modifications of endogenous GLP-1 (56). The longer-acting formulations are associated with dose-dependent reductions in HbA_{1c} and lowering of fasting (vs. post-prandial) reductions in glucose. The shorter-acting formulations are associated with greater post-prandial glucose lowering, likely mediated more by slowing of gastric motility as opposed to insulin release, as discussed in detail elsewhere (56,57). Large CV outcome trials have been completed

for 4 of the GLP-1 RA, all of which demonstrated noninferiority compared with placebo in T2D (6,7,9,47). However, only liraglutide (LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results]) and semaglutide (SUSTAIN-6 [Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes]) showed superiority in reducing MACE (6,7), as summarized in Figure 4. The CV benefit with liraglutide and semaglutide compared with placebo is unlikely to be driven by the modest glycemic difference between treatment and placebo groups (0.4% and 0.8% for liraglutide and semaglutide compared with placebo, respectively) (6,7), but rather a collection of favorable nonglycemic effects on CV risk factors including weight, blood pressure, lipids, and renal protection.

Weight. Liraglutide and semaglutide lowered weight by 2.3 and 3.6 kg more than placebo, respectively, in their CV outcome trials (6,7). This is slightly more weight than the ≈1.6- to 2.0-kg weight loss observed in the major SGLT2-i trials (5,8). The weight loss associated with GLP-1 RA is likely multifactorial and due to mechanisms leading to reduced caloric intake, as opposed to the glycosuric caloric loss associated with SGLT2-i (15). GLP-1 receptors in the hypothalamus and intestine have been implicated in the promotion of satiety, appetite suppression, and delayed gastric emptying, along with several adverse gastrointestinal side effects (e.g., nausea, vomiting, and diarrhea). Collectively, these effects result in consistent weight loss with GLP-1 RA use. A randomized controlled trial of 3,731 overweight to obese nondiabetic participants treated with once daily high-dose liraglutide (3.0 mg) demonstrated a mean 5.6-kg greater weight loss than the placebo group (58). In this trial, rates of progression from normoglycemia to pre-diabetes or pre-diabetes to T2D were also lower in patients treated with liraglutide. Importantly, there has been no significant hypoglycemia with GLP-1 RA use in trials enrolling diabetic (6,7) or nondiabetic participants (58).

Blood pressure. The LEADER and SUSTAIN-6 trials demonstrated modest systolic blood pressure reductions of 1.2 and 1.9 mm Hg more than placebo, respectively. The antihypertensive benefit could be related to GLP-1-induced atrial natriuretic peptide release by cardiomyocytes, resulting in improved endothelial function, vasodilatation, and natriuresis (48,59). Emerging evidence in animals also links GLP-1 agonism with improvement in cardiac efficiency in obesity and after myocardial infarction (60).
Lipids. GLP-1 RA agents can also exert favorable effects on lipid profiles (61), possibly through reduced post-prandial enterocyte chylomicron production.

FIGURE 4 Summary of Reductions in Major Adverse Cardiac Events in Recent GLP-1 RA Trials



Liraglutide and semaglutide significantly reduced MACE-3 in the 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) trials, respectively. Liraglutide significantly reduced CV death, heart failure hospitalization, and all-cause mortality. Semaglutide significantly reduced nonfatal stroke. ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; GLP-1 RA = glucagon-like peptide receptor agonist; other abbreviations as in Figure 2.

The increase in post-prandial insulin and reduction in glucagon can also lower nonesterified fatty acids and inhibit adipose tissue lipolysis (48,49), further improving lipid profiles. A large meta-analysis of 35 GLP-1 RA trials demonstrated modest reductions in total cholesterol, LDL cholesterol, and triglycerides (61). The more intensive dose of semaglutide in SUSTAIN-6 also lowered serum triglycerides (≈8 mg/dl) and free fatty acids (≈0.05 mmol/l) compared with placebo (7). This contrasts with the small increases in high-density lipoprotein (≈2 to 3 mg/dl) and LDL (≈3 to 4 mg/dl) observed in SGLT2-i outcomes trials compared with placebo (5,8).

Improvements in renal function. The mechanism underlying the renal benefits in LEADER and SUSTAIN-6 is not well understood. Treatment with liraglutide and semaglutide was associated with a 22% and 36% reduction in nephropathy (defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR below 45 ml/min/1.73 m² in both trials as well as the need for continuous renal replacement therapy in SUSTAIN-6), respectively, driven by a reduction in the incidence of new-onset persistent macroalbuminuria (6) (Figure 1). It is unclear if the renal benefit is due to direct GLP-1 RA effects on the kidney, or indirect effects on risk factors for nephrotoxicity (e.g., improved blood pressure and glycemic control). In vivo, animal, and human studies have also demonstrated other nonglycemic effects of GLP-1 RA, including anti-inflammatory properties, improved vascular endothelial function, ischemic conditioning, and antithrombotic effects via inhibition of platelet aggregation (48,62,63).

CLINICAL TRIAL EVIDENCE SUPPORTING GLP-1 RA USE FOR THE REDUCTION OF CVD. The LEADER trial randomized 9,340 patients with T2D to either the once-daily injectable 1.8 mg (or max tolerated dose) of liraglutide or placebo for a median follow-up of 3.8 years. The primary endpoint, MACE-3 including nonfatal MI, nonfatal stroke, and CV death, was significantly reduced in patients treated with liraglutide (HR: 0.87; 95% CI: 0.78 to 0.97), driven by a 22% significant reduction in CV death (HR: 0.78; 95% CI: 0.66 to 0.93) and nonsignificant reductions in nonfatal MI (HR: 0.88; 95% CI: 0.75 to 1.03) and nonfatal stroke (HR: 0.89; 95% CI: 0.72 to 1.11) (6) (Figure 4). There was also a significant 15% reduction in all-cause mortality (HR: 0.85; 95% CI: 0.75 to 0.97) along with a nonsignificant reduction in HF hospitalizations (6). The SUSTAIN-6 trial randomized 3,297 T2D patients to 2 doses of once-weekly injectable semaglutide (0.5 or 1.0 mg) or placebo for a median 2.1 years (7). Using the same MACE-3 composite, semaglutide was associated with a significant 26% reduction in the primary endpoint (HR: 0.74; 95% CI: 0.58 to 0.95) (7) (Figure 4). In contrast to LEADER, semaglutide did not reduce CV death (HR: 0.98; 95% CI: 0.65 to 1.48) or all-cause mortality (HR: 1.05; 95% CI: 0.74 to 1.50), but did demonstrate a significant reduction in nonfatal strokes (HR: 0.61; 95% CI: 0.38 to 0.99) and a nonsignificant trend toward fewer nonfatal MI (HR: 0.74; 95% CI: 0.51 to 1.08) (6,7) (Figure 4).

The trial participants in LEADER and SUSTAIN-6 were similar at baseline. Roughly 80% of participants in both trials had established stable CVD and an

average HbA_{1c} of 8.7% (6,7). Potential explanations for the lack of CV or all-cause mortality benefit in SUSTAIN-6 include the smaller trial population and nearly 2 years shorter follow-up duration than LEADER (6,7). Subgroup analyses of LEADER revealed heterogeneity for liraglutide treatment among patients with established CVD at baseline and those with impaired renal function (<60 ml/min/1.73 m²), although the distribution of benefit with liraglutide was not consistent among LEADER participants with impaired renal function (6,7).

Notably, a third GLP-1 RA agent, lixisenatide, did not demonstrate superiority in CV outcomes reduction in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial (47). In comparison to LEADER and SUSTAIN-6, enrollment in the ELIXA trial was restricted to T2D patients with a recent acute coronary syndrome (<180 days prior), randomizing 6,068 participants to once-daily injectable lixisenatide or placebo for a median follow-up of 2.1 years (47). ELIXA also added unstable angina hospitalization to the triple endpoint, but found no difference in the primary endpoint (HR: 0.94; 95% CI: 0.78 to 1.13), in any individual component, or in all-cause mortality (47). Compared with the other GLP-1 RA agents, lixisenatide has a shorter half-life (≈3 h), and demonstrated smaller effects on glycemic control (0.27% reduction in HbA_{1c}), systolic blood pressure, and weight reduction than either liraglutide or semaglutide (6,7,47). Although ELIXA participants had a recent acute coronary syndrome, they were younger, with lower systolic blood pressure and diabetes duration, and better glycemic control (entry HbA_{1c} 7.7%) compared with the other GLP-1 RA CV outcome trials. The rate of the primary endpoint (including unstable angina) in ELIXA (6.4 per 100 patient-years) was greater than that observed in LEADER, SUSTAIN-6, and the EXSCCEL (Exenatide Study of Cardiovascular Event Lowering) trial (3.9, 4.4, and 4.0 per 100 patient-years, respectively). (6,7,9,47)

Finally, a fourth GLP-1 RA agent, exenatide, in the largest GLP-1 RA CV outcomes trial to date, did not reach superiority for a reduction in CV outcomes compared with placebo (9). The EXSCCEL trial randomized 14,752 participants with T2D and established CVD to either the once-weekly injectable exenatide or placebo for a median follow-up of 3.2 years (9) for a MACE-3 composite outcome. The EXSCCEL trial demonstrated a nonsignificant trend toward benefit with exenatide (HR: 0.91; 95% CI: 0.83 to 1.00; *p* = 0.06 for superiority) (Figure 4). All-cause mortality was reduced by 14%, although due to hierarchical testing, this result is not considered statistically significant (9). Several trial design factors

and baseline patient selection may also explain the lack of superiority in EXSCEL. In comparison to LEADER and SUSTAIN-6, EXSCEL had a smaller proportion of participants with established CVD ($\approx 80\%$ vs. 73% , respectively) with better baseline glycemic control (HbA_{1c} 8.7% vs. 8.0%) (9). Furthermore, discontinuation of study drug (43.0%) and placebo (45.2%) may have limited power in the EXSCEL trial to detect a significant reduction in the primary endpoint.

Results from the long-acting GLP-1 RA trials with abiglutide (HARMONY Outcome; [NCT02465515](#)) and dulaglutide (REWIND; [NCT01394952](#)) will help clarify whether the CV benefit demonstrated by GLP-1 RA agents is a class effect (namely with the longer-acting, more potent agents) or a drug-specific effect only seen with liraglutide and semaglutide.

SAFETY CONCERNS WITH THE GLP-1 RECEPTOR AGONISTS. Both the LEADER and SUSTAIN-6 trials have illuminated potential deleterious effects associated with GLP-1 RA use, including the risk for retinopathy, acute gallstone disease ([Figure 3B](#)), and increased heart rate.

In SUSTAIN-6, semaglutide was associated with a significantly increased risk of retinopathy (3.0%) (7). In the LEADER trial, retinopathy was numerically more common among participants randomized to liraglutide (2.3%) than to placebo (2.0%), but this difference was nonsignificant (6) ([Figure 3B](#)). Reassuringly, a large meta-analysis of 37 GLP-1 RA trials of 21,782 participants with diabetes treated with GLP-1 RA did not find a meaningful increase in retinopathy events (64), suggesting that retinopathy may be a semaglutide-specific drug effect or a type I error, rather than a class effect. The pathological mechanism behind the retinopathy complications is unclear. A previous study noted that rapid glucose lowering with insulin among patients with type 1 diabetes was associated with worsening of retinopathy (65), but the applicability of this finding is unclear.

The LEADER trial demonstrated a greater incidence of acute gallbladder disease with liraglutide (3.1%) compared with placebo (1.9%), a finding that was also numerically greater with semaglutide (3.6%) in SUSTAIN-6 ([Figure 3B](#)). A similar observation was made in a large population-based cohort study in patients treated with exenatide or liraglutide with or without other glucose-lowering agents (66). The mechanism of this side effect is likely multifaceted, possibly related to rapid weight loss leading to supersaturation of bile acid cholesterol, impaired gallbladder emptying, and cholangiocyte proliferation (66). Despite previous concerns regarding pancreatitis and medullary thyroid cancer risk associated

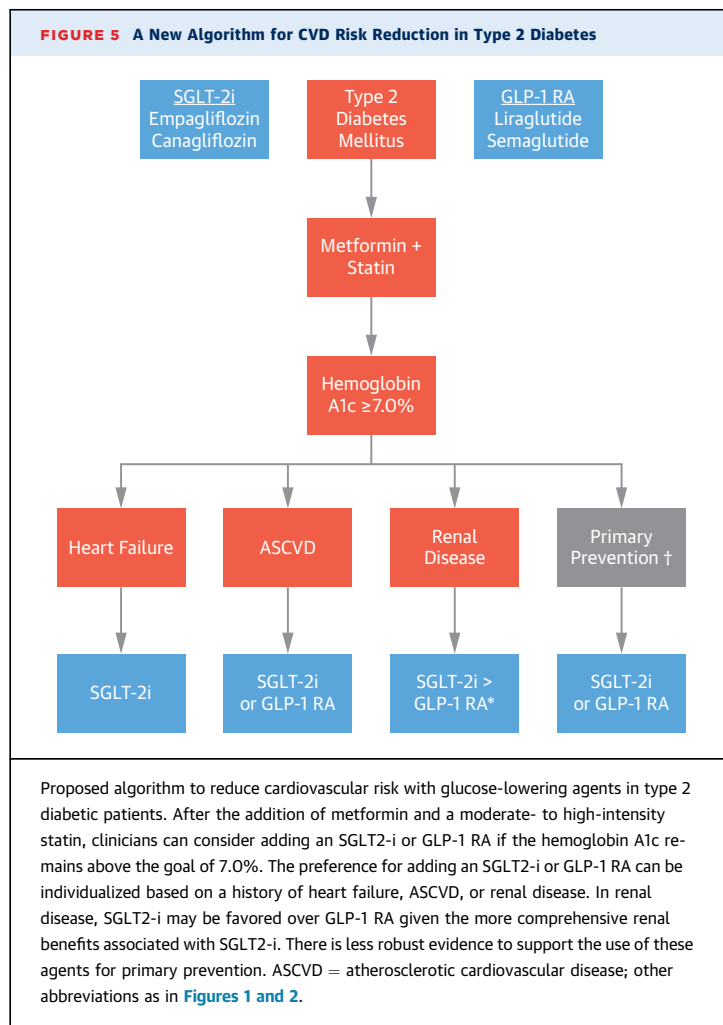
with GLP-1 RA use (67), this was not substantiated in LEADER, SUSTAIN-6, or a recent meta-analysis of all 4 CV outcome trials combined (68).

GLP-1 RA use is also associated with increased heart rate, especially with the long-acting formulations, although the mechanism has yet to be elucidated (69). In the FIGHT (Functional Impact of GLP-1 for Heart Failure Treatment) trial, a blinded, randomized phase 2 study of 300 hospitalized patients with systolic heart failure (approximately 60% of whom had concomitant T2D), there was a 30% nonsignificant increased risk of rehospitalization for heart failure in participants treated with liraglutide (70). Although LEADER demonstrated numerically, albeit nonsignificantly, fewer heart failure hospitalizations, only 18% of the trial population had chronic heart failure (New York Heart Association functional class II or III) at baseline (6). In SUSTAIN-6, nearly 24% of participants had chronic heart failure (New York Heart Association functional class II or III) at trial entry, and randomization to semaglutide was associated with a numerically greater but statistically nonsignificant increase in the risk of heart failure hospitalization (7). Hence, although GLP-1 RA are not contraindicated in patients with heart failure, therapeutic alternatives such as the SGLT2-i appear to have more demonstrable benefit among diabetic patients with a history of heart failure.

BACKGROUND MEDICAL THERAPY AND RISK FACTOR CONTROL IN CV OUTCOME TRIALS

CV risk factors, such as smoking, hypertension, and dyslipidemia, independently contribute to CVD risk in T2D patients (2,71). Several CV risk factors contribute to the development of T2D, and patients with T2D have a higher prevalence of CV risk factors (72). Treatment of CV risk factors in T2D prevents and slows CVD progression, especially when multiple risk factors are addressed simultaneously (2,73–75). However, almost one-half of U.S. adults with T2D still do not achieve goals for CV risk reduction (4). When evaluating the efficacy of the newer glucose-lowering agents, it is important to consider background medical therapy and risk factor control in these trials.

Online Figure 1 presents the mean baseline systolic blood pressure (SBP), body mass index, and LDL cholesterol for participants in the 4 major CV outcome trials reviewed (5–8). At trial entry, participants had a mean SBP >135 mm Hg, a body mass index >30 kg/m², and an LDL cholesterol >80 mg/dl. As shown in Online Figure 2, roughly 25% to 30% of patients in these trials were not on a statin at baseline despite



guideline recommendations to treat T2D with moderate- to high-intensity statins (71,76). Subgroup analyses from EMPA-REG, the CANVAS Program, LEADER, and SUSTAIN-6 showed that active treatment reduced CV events regardless of baseline risk factor control. Overall, background medical therapy for CVD prevention in these trials was similar to or exceeds that seen in current clinical practice (4). Recent analyses of SGT2-i use in clinical practice suggests a magnitude of benefit comparable to that observed in recent clinical trials (41,42).

Baseline metformin, sulfonylurea, and insulin use was similar for participants in EMPA-REG, CANVAS Program, LEADER, and SUSTAIN-6 (Online Figure 2A). Among trials that reported post-randomization changes in glucose-lowering therapies (EMPA-REG, LEADER, and SUSTAIN-6), insulin use increased significantly in the placebo arm versus active comparator (5-8) (Online Figure 2B). Sulfonylureas

and insulin can lead to weight gain and potentiate hypoglycemia, both of which are associated with increased CVD morbidity and mortality (77,78). Although participants randomized to SGLT2-i or GLP-1 RA lost more weight than those receiving placebo, weight for the placebo arm did not increase. Moreover, there was no significant difference in episodes of severe hypoglycemia between active treatment and placebo in these 4 trials (8). These findings suggest that post-randomization confounding by increased use of glucose-lowering therapies with adverse side effect profiles is unlikely to explain the magnitude of outcome benefit observed (79).

APPLICATION OF NEW THERAPIES TO PRIMARY OR SECONDARY PREVENTION

A key question moving forward will be whether the reduction in CVD events observed with SGLT2-i and GLP-1 RA among T2D patients with established CVD is applicable to the primary prevention of CVD in T2D patients with multiple CVD risk factors. On the one hand, as reviewed, one potential explanation for the lack of mortality benefit in the CANVAS Program and failure of the EXSCEL trial to demonstrate superiority for CV outcomes may be the larger populations of lower-risk T2D patients enrolled compared with trials that enrolled populations at higher CVD risk (8,9). Heterogeneity of treatment effect was also observed with liraglutide, favoring its use in T2D patients with established CVD (6). On the other hand, a recent secondary analysis from the CANVAS Program did not demonstrate heterogeneity of treatment effect with canagliflozin across the primary and secondary prevention groups (80). The ongoing DECLARE-TIMI-58 (Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis In Myocardial Infarction 58) trial with dapagliflozin will be the largest SGLT2-i trial to date, with nearly 60% of the study population in a primary prevention cohort (31). DECLARE-TIMI 58 will provide crucial data about expanding the use of these glucose-lowering agents to a lower-risk, larger population of T2D patients.

Because the glucose-lowering effects of SGT2-i and GLP-1 RA appear to be in part dependent on glucose concentration, and the risk of hypoglycemia is very low, the potential that these agents could be used to lower elevated CVD risk among patients with metabolic syndrome or pre-diabetes is appealing. In fact, GLP-1 RA have demonstrated efficacy for weight loss and improvement in CV risk factors among obese nondiabetic and pre-diabetic patients (58). High-dose liraglutide was also demonstrated in this trial to delay the onset of T2D (58).

A NEW TREATMENT PARADIGM AND FUTURE DIRECTIONS

We have reviewed the remarkable advances that the recent CV outcomes trials with SGLT2-i and GLP-1 RA represent for patients with diabetes and health care providers, including cardiologists. **Figure 5** presents a treatment algorithm encapsulating these recent studies and indicates potential future directions. There are a few issues worth highlighting from **Figure 5** and directions forward.

First, all recent CV outcome trials reviewed were completed on a background of metformin therapy, along with other glucose-lowering agents (**Online Figure 2A**). Until the completion of these recent trials, metformin was the only drug with evidence for CV benefit, albeit in very modest numbers of patients with small number of events and relatively low event rates (81). As noted (11), metformin does not cause weight gain or increase risk of hypoglycemia, has many years of safety evidence, and is inexpensive. Therefore, metformin is justifiably used as a first-line therapy for T2D patients with and without established CVD. However, the thousands of patients enrolled in these recent CV outcomes trials dwarf the number included in the landmark UK Prospective Diabetes Study (81). Whether or not metformin background therapy is warranted with concomitant use of SGLT2-i or GLP-1 RA is not entirely certain, and is worthy of future investigation. It is also worth exploring the outcome benefits of SGLT2-i and GLP-1 RA use among patients with diabetes under better glucose control at baseline; participants in the trials reviewed had an average baseline HbA_{1c} over 8%.

Second, very limited data exist on the use of SGLT2-i and GLP-1 RA in combination. Recent data with the combination of 10 mg daily oral dapagliflozin with once-weekly subcutaneous 2 mg exenatide among patients with poor glycemic control on metformin monotherapy demonstrated improved glycemic control, weight loss, and lower SBP (82). However, data is needed on the combination of these agents for reduction of CV events. A recent network meta-analysis indicates that compared with GLP-1 RA and DPP4 inhibitors, SGLT2-i were most likely to rank best for all-cause and CV mortality, along with heart failure and MI outcomes (83). GLP-1

RA ranked best for stroke reduction, but had increased side effects leading to study drug termination compared with SGLT2-i (83). A comparative effectiveness trial of these 2 agents, with or without background metformin therapy, may be highly informative.

Third, the use of SGLT2-i and GLP-1 RA warrant dedicated randomized trial-level investigation of their effects among T2D patients with reduced eGFR and objectively determined heart failure at baseline. As indicated in this review, there are several ongoing trials in this area that will hopefully shed light on the use of these new agents in critically important patient populations at elevated risk of CV morbidity and mortality.

Finally, we need to examine the potential benefit of these agents for patients with disordered glucose metabolism, including pre-diabetes or metabolic syndrome. It has been shown that the vascular effects of disordered glucose metabolism begin significantly before the diagnostic threshold for diabetes has been reached (84). The trials reviewed show overall reductions in CV outcomes likely independent of their effects on glycemic control (5-8). Moreover, the glucose-lowering effects of SGLT2-i and GLP-1 RA are glucose-dependent, with very low if any risk of hypoglycemia. Therefore, the study of these agents among patients with pre-diabetes or metabolic syndrome, with established CVD or multiple CVD risk factors, may be a transformative use of these medications and a method toward primordial CV risk reduction among patients with abnormal glucose metabolism. The experience of statins for the secondary prevention of CVD regardless of baseline LDL (85), or for the primary prevention of CVD (86), may provide a useful paradigm to guide future studies of these agents in the growing population of individuals who are at elevated risk for T2D.

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APPENDIX For supplemental figures, please see the online version of this paper.