THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Novel Diabetes Drugs and the Cardiovascular Specialist

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ABSTRACT

Recently, treatment with 2 newer classes of type 2 diabetes drugs were found to reduce events in patients with diabetes and cardiovascular (CV) disease, a group common in cardiology clinics. The sodium-glucose cotransporter 2 inhibitor, empagliflozin, markedly and rapidly reduced CV death and heart failure hospitalization, likely with hemodynamic/metabolic-driven mechanisms of action. More recently, the glucagon-like peptide-1 receptor agonists liraglutide and semaglutide also reduced CV death and/or major adverse CV events, but did so more slowly and did not influence heart failure risks, suggesting alternative mechanisms of benefit. We will discuss drug therapy for diabetes relative to CV risk, briefly summarize key findings of CV benefit from recent trials, discuss potential mechanisms for benefits of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 agonists, and suggest how such drugs might be embraced by CV specialists to reduce CV events and mortality in their patients. (J Am Coll Cardiol 2017;69:2646–56) © 2017 by the American College of Cardiology Foundation.

Most cardiologists have focused their efforts on managing traditional risk factors, and have paid less attention to type 2 diabetes (T2D) therapies whose primary role is to lower glucose. This may be because, until recently, T2D therapies other than metformin had little obvious favorable effect on cardiovascular (CV) outcomes, the principal cause of morbidity and mortality in T2D. Indeed, for cardiologists, the most common diabetes drug intervention was to stop drugs that may cause heart failure (e.g., glitazones);

initiation or titration of drugs for diabetes care was most commonly referred to primary caregivers or diabetes specialists. If anything, concerns about CV safety were more prevalent than reassurance as to the potential benefits of these agents.

THE RISE OF CV SAFETY AND OUTCOME TRIALS IN DIABETES CARE

In light of concerns regarding CV safety of new glucose-lowering drugs being developed, the U.S.

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Food and Drug Administration (FDA) and European Medicines Agency mandated that new therapies for diabetes had to demonstrate CV safety in prospective, randomized controlled outcome trials. Current recommendations for trial design of new therapies for T2D have been recently reviewed (1) and include iterative assessment of drug safety, with initially liberal pre-approval statistical boundaries to exclude unacceptable CV risk, followed by more restrictive boundaries post-approval. For phase 4 post-marketing outcome trials, ultimately, the upper bound of the 95% confidence interval (CI) for any T2D treatment should not exceed 1.30 for major adverse cardiovascular events (MACE), whereas a 1.80 upper limit applies to phase 3 trials. Additionally, the recommendation was made that trials evaluating novel T2D therapies should focus on high-risk populations (such as those with vascular disease, with renal impairment, or at advanced age) and should include long-term data, and that all MACE events measured in such trials should be adjudicated by an independent committee.

Although designed to detect a risk signal, remarkably, results from recent "cardiovascular outcomes trials" (CVOTs) may lead to a meaningful change in how cardiologists might approach the patient with T2D, as these CVOTs have shown not only CV safety, but also reduced CV and all-cause mortality in some studies (2-4). These trials include patients who are common to cardiologists' practices, and the magnitude of the results compares favorably with the landmark cardiology trials that have shaped our international cardiology guidelines (5,6).

Clearly, cardiologists would do well to keep up with this evolving area of T2D CVOTs to ensure that their patients potentially benefit from newer therapies for diabetes care. In addition, a good understanding of the potential risks of diabetes drugs in treating patients with CV disease is also important. Before discussing newer therapies, reviewing experience of the CV effects of older drugs is helpful.

DIABETES DRUGS THAT HAVE LESS FAVORABLE OR UNCERTAIN CV OR MORTALITY RISK BENEFITS

Although meta-analyses of landmark glucose-lowering trials suggest that intensive glycemic control does reduce risk for CV disease events (7), improved CV outcomes as a function of intensive glucose control appear modest in comparison to the calculated CV benefits from lipid and blood pressure management (8). In addition, some concerning signals for risk of CV events have been associated with certain widely-used diabetes medications, including sulfonylureas, thiazolidinediones, dipeptidylpeptidase 4 inhibitors, and insulin.

SULFONYLUREAS. Although widely used for care of T2D, drugs from the sulfonylurea class of drugs (although perhaps less so for gliclazide) (9) have been associated with a higher risk for CV events, notably including a higher risk for nonfatal myocardial infarction (MI) or CV death, relative to other diabetes drugs (10). For example, a meta-analysis of 72 small or modest-sized randomized controlled trials found that all-cause mortality; CV mortality; and a composite of MI, stroke, and CV mortality were all increased in patients treated with glibenclamide, glipizide, and tolbutamide compared with metformin (11). Based on these and other data, sulfonylurea medications carry a "black box" CV warning from the FDA regarding heightened risk for CV events, although the same is not true in many non-U.S. countries.

THIAZOLIDINEDIONES. Thiazolidinediones (TZDs) are agonists for the peroxisome proliferator-activated receptors that regulate gene expression, resulting in improved glucose utilization and reduced glucose production. TZDs improve a number of CV risk factors and became widely used at one point; however, reports of potential CV risk (including reports of fluid retention with incident heart failure as well as a possible increased risk for incident MI [12]), and earlier reports of excess bladder cancer risk (now debated [13]) led to reduction in their use. For example, the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial reported an adjusted risk for incident heart failure (hazard ratio [HR]: 2.25; 95% CI: 1.27 to 3.97) (14), similar to findings in a meta-analysis (15). The MI risks for rosiglitazone have now been largely dispelled (16), whereas pioglitazone does have trial evidence to show net CV benefit (17), but the heightened heart failure risk, as well as weight gain and potential risks for fractures with this class of drugs, has led to a reduction in their use (18).

DIPEPTIDYL PEPTIDASE-4 INHIBITORS. Dipeptidyl peptidase-4 (DPP-4) is an enzyme that degrades many peptides, including glucagon-like peptide (GLP)-1; thus, pharmacological inhibition of DPP-4 prolongs the half-life and biological activity of GLP-1. Inhibitors of DPP-4 have modest glucose-lowering effects, but although 3 recent CVOTs did show evidence of CV safety according to FDA criteria, they did not demonstrate net CV benefits (19-21) contradicting an earlier meta-analysis (22). Furthermore,

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CV = cardiovascular

CVOT = cardiovascular outcomes trial

GLP = glucagon-like peptide

HbA$_{1c}$ = glycosylated hemoglobin

HR = hazard ratio

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

SGLT = sodium-glucose cotransporter

T2D = type 2 diabetes

TABLE 1   Summary of Key Findings of the 3 Positive CVOTs in T2D, Detailing Adverse Effects and Broad Beneficial Mechanisms Implicated in CV Benefits

	EMPA-REG OUTCOME (2)	LEADER (3)	SUSTAIN-6 (4)
Agent	Empagliflozin (SGLT2 inhibitor)	Liraglutide (once-daily GLP-1 agonist)	Semaglutide (once-weekly GLP-1 agonist)
Inclusion criteria	All with T2D and CVD HbA$_{1c}$ 7%–10%	Age >50 yrs with CVD or >60 yrs with ≥1 CV risk factor HbA$_{1c}$ >7%	Age >50 yrs with CVD or >60 yrs with ≥1 CV risk factor HbA$_{1c}$ >7%
Duration of trial	3.1 yrs	3.8 yrs	2.05 yrs
Baseline HbA$_{1c}$	8.1%	8.7%	8.7%
Primary endpoint	↓ 14% (1% to 26%)	↓ 13% (3% to 22%)	↓ 26% (5% to 42%)
CV death	↓ 38% (23% to 51%)	↓ 22% (7% to 34%)	↓ 2% (−48% to 35%)
MI	↓ 13% (−9% to 30%)	↓ 12% (−3% to 25%)	↓ 26% (−8% to 49%)
Stroke	↑ 24% (−8% to 67%)	↓ 11% (−11% to 28%)	↓ 39% (1% to 72%)
HF hospitalization	↓ 35% (15% to 50%)	↓ 13% (−5% to 27%)	↑11% (−23% to 61%)
Noteworthy adverse effects	Genitourinary infections, no excess DKA	More gallstones, GI side effects	Higher retinopathy rates
Likely broad mechanisms of benefit	Rapid effects suggest a hemodynamic or metabolic benefit, although a vascular benefit may also occur	Slower effects suggest benefits via less atherothrombosis and/or avoidance of hypoglycemia	Slower effects suggest benefits via less atherothrombosis

↓ = decrease; ↑ = increase; CV = cardiovascular; CVOT = cardiovascular outcomes trials; DKA = diabetic ketoacidosis; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA$_{1c}$ = glycosylated hemoglobin; HF = heart failure; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes-6.

because of recent data suggesting a higher risk for incident heart failure associated with use of saxagliptin and alogliptin, recent regulatory warnings have been put in place for these 2 agents. Although meta-analyses suggest the risk for incident heart failure to be significant with this class of drug (relative risk: 1.13; 95% CI: 1.01 to 1.26) (23), not all DPP-4 inhibitors have been linked to heart failure risk; for example, recent data suggest no increased risk for incident heart failure related to sitagliptin use (24).

INSULIN. Insulin is effective for glucose lowering and is very widely used for the treatment of advanced T2D. Therapy with insulin commonly leads to increased body weight and is associated with greater hypoglycemia risks. Thus, although insulin might improve glycemic control, its other effects may theoretically attenuate its clear glucose-lowering benefits in subgroups with particular susceptibility to hypoglycemia or the adverse effects of hypoglycemia. There was also some expectation that exogenous insulin administration early in the course of T2D may have beneficial effects on CV outcomes; however, the results of the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial failed to demonstrate any CV benefit (25).

DIABETES DRUGS RECENTLY REPORTED TO REDUCE CV AND CV MORTALITY RISK

Although numerous therapies for T2D have been associated with an increased risk of CV events, 3 recent CVOTs have shown benefit in terms of hard clinical endpoints (**Table 1**) (2-4). We first review the results for the sodium-glucose cotransporter (SGLT) 2 inhibitor, empagliflozin, before discussing results for 2 GLP-1 receptor agonists.

Of course, it should be noted that up until these recent trials, metformin was the only drug with possible evidence for CV benefit, albeit in very modest numbers of patients and with low event numbers. In the UKPDS (UK Prospective Diabetes Study), metformin-treated patients had a 30% lower risk for macrovascular disease than did patients not given metformin (26). Importantly, metformin does not cause weight gain or increased risk for hypoglycemia, has many years of safety evidence, and is inexpensive; thus, it is widely used as a first-line therapy for the patient with CV disease.

SGLT2 INHIBITORS. SGLT2 is a low-affinity, high-capacity glucose transporter located in the proximal tubule of the nephron; SGLT2 is responsible for 90% of glucose reabsorption. Inhibition of SGLT2 results in decrease of blood glucose due to glycosuria. Secondary effects of SGLT2 inhibition include a modest diuretic effect (sodium loss is also promoted), weight loss, and lowering of blood pressure.

The only available CVOT for SGLT2 inhibitors recently reported reduction in CV events following treatment with empagliflozin compared with placebo. The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial included 7,020 patients with

FIGURE 1 Comparing and Contrasting the Outcome Benefits in the EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 Trials
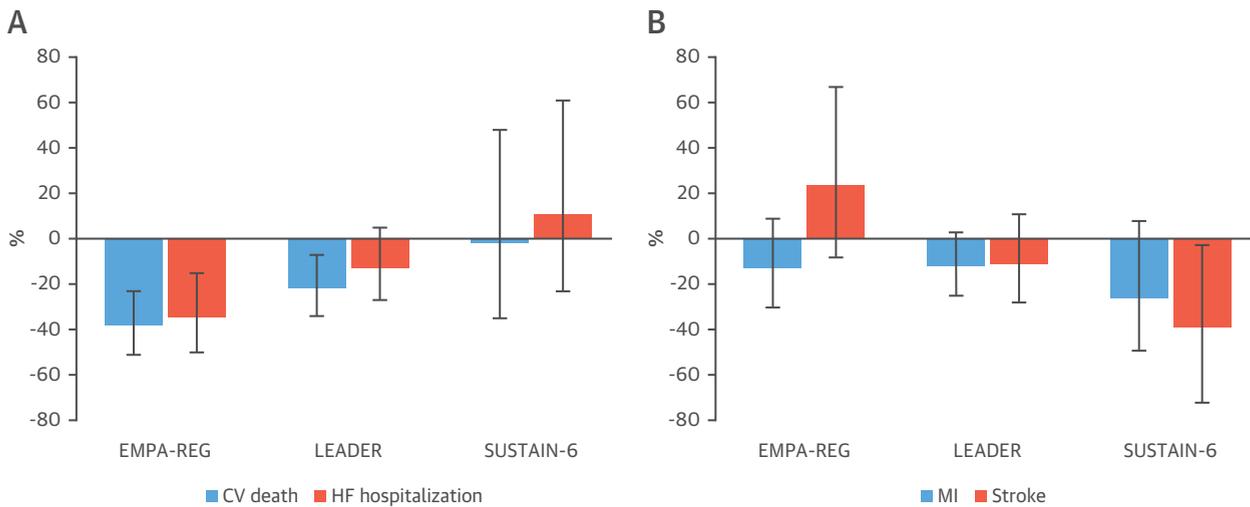
(A) Cardiovascular death and heart failure hospitalization. In the EMPA-REG OUTCOME trial, the most marked benefit was seen on reduction in CV death and heart failure hospitalization, with a more modest benefit in LEADER on cardiovascular death, and little evidence for such benefits in SUSTAIN-6. One must be careful to note that event numbers in the latter trial were small, in keeping with much larger confidence intervals. (B) Acute myocardial infarction and stroke. Greatest reductions in these events were seen in SUSTAIN-6 (although, once again, small event numbers suggest caution in interpretation), whereas such benefits were more modest in LEADER (although directionally similar). By contrast, such effects in EMPA-REG OUTCOME were mixed, although once again caution is needed, given overlapping confidence intervals. CV = cardiovascular; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HF = heart failure; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI = myocardial infarction; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes-6.
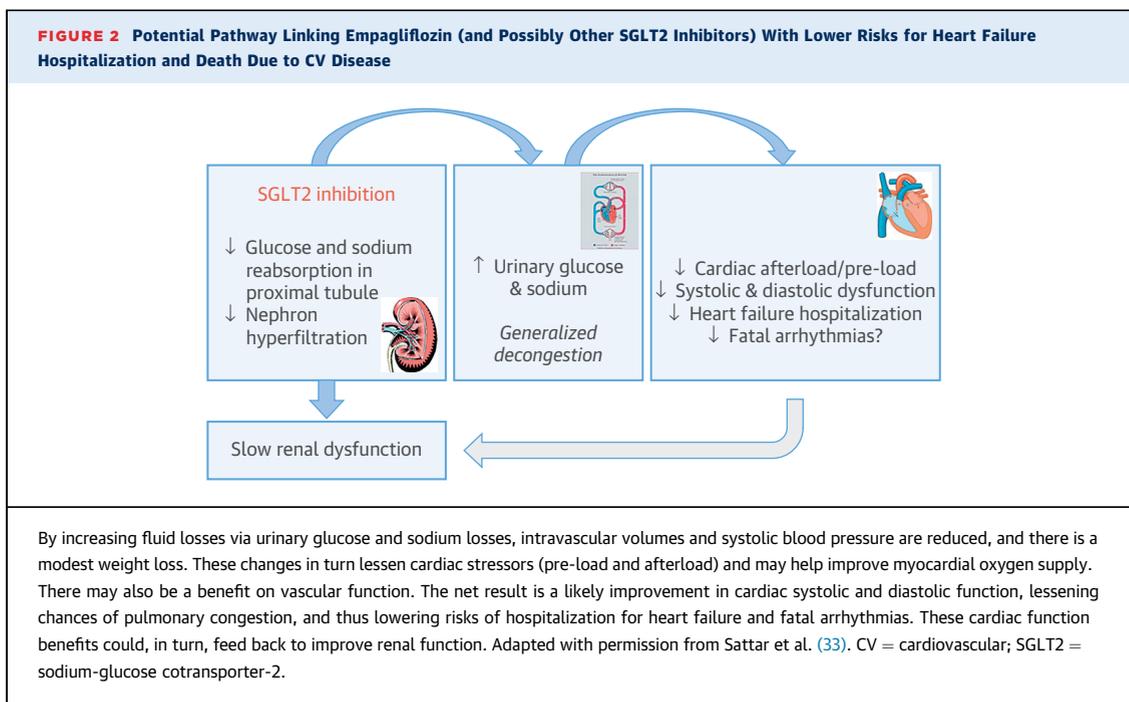
established CV disease, and randomized them to placebo, empagliflozin 10 mg, or empagliflozin 25 mg. All study participants had established CV disease. The primary endpoint of EMPA-REG OUTCOME was 3-point MACE (CV mortality, nonfatal MI, and nonfatal stroke). Patients randomized to empagliflozin had a modest reduction in the primary endpoint (HR: 0.86; 95% CI: 0.74 to 0.99; p = 0.04 for superiority; absolute risk reduction [ARR]: 1.6%). The reduction in the primary endpoint was driven predominately by a substantial reduction in CV death (HR: 0.62; 95% CI: 0.49 to 0.77; p < 0.001; ARR: 2.2%), whereas nonfatal MI and stroke were not significantly altered; a 32% reduction in all-cause mortality was also observed (**Figures 1A and 1B**). Interestingly, benefit from empagliflozin in EMPA-REG OUTCOME was similar between the 2 doses tested. In recognition of the statistically robust effect on CV mortality, the FDA recently granted an indication to empagliflozin to reduce risk for CV death (27).

Notably, in EMPA-REG OUTCOME, heart failure hospitalization was reduced by 35% (HR: 0.65; 95% CI: 0.50 to 0.85; p = 0.002; ARR 1.4%), with a rapid separation in the survival curves suggesting acute benefit of the drug. The reduction in heart failure

events was particularly clinically relevant, as drugs from other classes of glucose-lowering drugs with very different mechanisms of action (in particular, saxagliptin and rosiglitazone) had previously been found to be associated with an increase in hospitalizations for heart failure (15,19).

Although compelling, there are several reasons why heart failure outcome results should be interpreted cautiously. Although hospitalization for heart failure was a pre-specified outcome in EMPA-REG OUTCOME, it was not the primary outcome and did not have the rigor characteristic of heart failure trials. Patients could be recruited on the basis of investigator-reported heart failure, but there was no formal assessment of heart failure status, or cardiac structure or function at baseline; for example, no natriuretic peptide measurement or echocardiography was performed. No understanding regarding forms of heart failure (e.g., preserved vs. reduced ejection fraction) was established. Furthermore, it is possible that some of the 76% of patients included on the basis of coronary artery disease at baseline (including 47% with prior MI) may have had unrecognized left ventricular dysfunction.

In short, the finding of reduced hospitalization for heart failure is impressive, but further detail

FIGURE 2 Potential Pathway Linking Empagliflozin (and Possibly Other SGLT2 Inhibitors) With Lower Risks for Heart Failure Hospitalization and Death Due to CV Disease

SGLT2 inhibition

↓ Glucose and sodium reabsorption in proximal tubule
↓ Nephron hyperfiltration

↑ Urinary glucose & sodium

Generalized decongestion

↓ Cardiac afterload/pre-load
↓ Systolic & diastolic dysfunction
↓ Heart failure hospitalization
↓ Fatal arrhythmias?

Slow renal dysfunction

By increasing fluid losses via urinary glucose and sodium losses, intravascular volumes and systolic blood pressure are reduced, and there is a modest weight loss. These changes in turn lessen cardiac stressors (pre-load and afterload) and may help improve myocardial oxygen supply. There may also be a benefit on vascular function. The net result is a likely improvement in cardiac systolic and diastolic function, lessening chances of pulmonary congestion, and thus lowering risks of hospitalization for heart failure and fatal arrhythmias. These cardiac function benefits could, in turn, feed back to improve renal function. Adapted with permission from Sattar et al. (33). CV = cardiovascular; SGLT2 = sodium-glucose cotransporter-2.

documenting the patient characteristics and biomarkers of heart failure is unavailable. It is possible that in some cases empagliflozin prevented the onset of clinical heart failure in those with unrecognized left ventricular dysfunction, but also that in some cases empagliflozin-treated patients already had unrecognized clinical heart failure. Mechanistic, or "bedside to bench," studies are now trying to clarify the mechanistic relationship between empagliflozin and heart failure, while large outcome trials investigating the possible efficacy of SGLT2 inhibitors in treating heart failure with both preserved and reduced ejection fraction are also underway (28-30).

Other benefits seen in EMPA-REG OUTCOME may help to clarify the effect of empagliflozin on CV outcomes. For example, empagliflozin also had a favorable effect on renal endpoints (31), with reduction in incident or worsening nephropathy and incident albuminuria. Whether these beneficial renal effects are secondary to improved perfusion by cardiac or cardiovascular mechanisms or whether they are due to primary renal effects is unknown, although most consider renal benefits (thought to reflect reversal of maladaptive tubulo-glomerular renal feedback) to be largely upstream.

The mechanism of benefit of empagliflozin is not fully known, but several are speculated (**Figure 2**). As noted, empagliflozin has numerous possibly beneficial CV effects including the hemodynamic effects of a diuretic agent; beneficial renal (reduction in

intraglomerular pressure) (32), blood pressure, and weight effects; as well as many others, as recently reviewed (33,34). Most experts believe the rapid reduction in CV death and heart failure hospitalizations seen in EMPA-REG OUTCOME is best explained by a rapid hemodynamic effect (34,35). Natriuresis, in combination with renal glucose losses, is thought to lead to a reduction in circulating volume and possibly extracellular fluid load, with a consequent lowering of cardiac filling and pre-load and afterload pressures. Supporting this concept was the rapid and sustained increase in hemoglobin and hematocrit demonstrated in EMPA-REG OUTCOME (2), as well as preliminary evidence for empagliflozin-induced improvements in left ventricular mass and diastolic function (36).

In a more general sense, the data from EMPA-REG OUTCOME suggest that many patients with T2D and CV disease may have previously unrecognized excessive fluid overload, often in association with cardiac dysfunction, and that these patients benefit rapidly from intravascular decongestion. Some have suggested that less left ventricular stretch, arising from corrections in intravascular fluid load, might also decrease the incidence of atrial and ventricular arrhythmias. Another potential mechanism of benefit is that patients randomized to empagliflozin were less likely to receive other glucose-lowering therapies (e.g., insulin and sulfonylureas), drugs that increase weight and hypoglycemia risks. Possibly, avoidance of these therapies in the treatment arm could have

contributed to the positive outcome. A further proposed mechanism of benefit of empagliflozin, the ketone hypothesis, has been proposed, whereby slightly increased ketones with SGLT2 inhibitors serve as a better fuel supply for the failing heart (37).

It is important to understand the potential side effects of SGLT2 inhibitors. The most notable adverse effect in EMPA-REG OUTCOME was an absolute 4.6% increase in genital infections; a greater incidence was noted in women. Fortunately, these infections are not generally serious, and resolve with a course of antifungal agents. Once treated, they uncommonly recur. From the perspective of a cardiologist, patients should be informed of this risk, and shared care with primary care physicians (who manage these conditions on a regular basis) is recommended. It would not be prudent to use SGLT2 inhibitors in women or men with a history of recurrent genital infections. In EMPA-REG OUTCOME, there was no increase in urinary tract infections, hypoglycemic episodes, or diabetic ketoacidosis. Some concern does remain as to whether or not SGLT2 inhibitors can increase the risk of diabetic ketoacidosis outside of the tightly monitored environment of a clinical trial, particularly in patients with T2D treated with insulin. It should be noted that cases of ketoacidosis have been reported in the off-label use of SGLT2 inhibitors in patients with type 1 diabetes (38). Patients given these agents should be educated about simple warning signs and symptoms of potential diabetic ketoacidosis.

It is worthwhile to emphasize that EMPA-REG OUTCOME was not a primary prevention trial. Although tempting to speculate, it is impossible to conclude that similar benefits would be seen in patients without CV disease. This makes the results of EMPA-REG OUTCOME all the more important to the practicing cardiovascular specialist, given the high prevalence of T2D in those with established CV disease (39). Several other similar safety trials are being conducted with SGLT2 inhibitors with slightly differing pharmacology. However, these trials also differ in size and patient composition. For example, 60% of participants in DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis In Myocardial Infarction 58) (NCT01730534) do not have prior CV disease, which is important. These trials will report results over the next few years.

GLP-1 RECEPTOR AGONISTS. Following on from empagliflozin, 2 other drugs, both from the GLP-1 receptor agonist family, have been shown to improve CV outcomes, albeit in a different pattern than EMPA-REG OUTCOME (**Figures 1A and B**).

Liraglutide is a once-daily injectable GLP-1 receptor agonist. It is also associated with weight loss and blood pressure lowering. In the recent LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, 9,340 patients with a glycosylated hemoglobin (HbA$_{1c}$) of >7.0% (either >50 years of age with established CV disease or >60 years of age with 1 or more CV risk factors) were randomized to liraglutide or placebo (3). The primary endpoint of MACE was reduced by 13% (HR: 0.87; 95% CI: 0.78 to 0.97; ARR 1.9%; p for superiority = 0.01). The components of the primary endpoint were all numerically in favor of liraglutide, but only CV mortality was statistically significantly reduced (HR: 0.78; 95% CI: 0.66 to 0.93; p = 0.007; ARR 1.3%); all-cause mortality was also reduced (HR: 0.85; 95% CI: 0.74 to 0.97). Subgroup analysis did suggest a greater benefit in those with established CV disease, rather than those with risk factors in the absence of clinically-evident disease. Nephropathy events were less common with liraglutide (1.5 vs. 1.9 per 100 patient-years) but, in contrast to the widespread renal benefits with empagliflozin, liraglutide-driven renal benefits were driven largely by a reduction in new-onset persistent macroalbuminuria, with little discernible effects on other renal outcomes.

Subsequently, SUSTAIN (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes)-6 investigated the safety of the once-weekly GLP-1 receptor agonist, semaglutide. In this phase 3, randomized, placebo-controlled noninferiority trial, 3,297 study participants were treated with semaglutide or placebo. The inclusion criteria were very similar to those used in the LEADER trial, as was the primary endpoint of 3-point MACE. Treatment with semaglutide reduced the primary endpoint by 2.3% (HR: 0.74; 95% CI: 0.58 to 0.95; p < 0.001 for noninferiority; p = 0.01 for superiority). The contribution of the components of MACE to the reduction in the primary endpoint was somewhat different to that seen in the LEADER trial, in that CV mortality was not affected by semaglutide, but nonfatal stroke was improved (ARR: 1.1%; HR: 0.61; 95% CI: 0.38 to 0.99) along with a nonsignificant trend toward lower rates of incident MI (**Figures 1A and 1B**). It is important to draw an important distinction between the LEADER and SUSTAIN-6 trials, as the latter study had a much smaller noninferiority design, increasing risk for type 1 and type 2 error due to underpowering.

It is not yet understood how GLP-1 receptor agonists may reduce CV events. Compared with trials of SGLT2 inhibitors, the relative benefit of GLP-1

agonists appeared at a later time following randomization, in line with atherothrombotic, rather than hemodynamic effects. However, both MI and stroke were numerically, but not statistically, lower with liraglutide than with placebo in the LEADER trial. If this was the predominant mechanism of action explaining LEADER results, a more convincing reduction in MI or stroke might have been anticipated. Other possible mechanisms are blood pressure reduction, lessening of arterial stiffness (in keeping with lower systolic blood pressure, but higher diastolic blood pressure, so narrowing of pulse pressure), weight loss, and beneficial renal effects. The reduction in blood glucose was more pronounced in the early years in the LEADER trial than in other recent diabetes CVOTs, so one cannot rule out that glucose lowering contributed to its beneficial effects; patients randomized to liraglutide were less likely to be exposed to insulin or sulfonylureas, prompting speculation that preventing exposure to these potentially harmful (or less "net" beneficial) drugs in such patients may also be a contributory mechanism. As well, severe hypoglycemia was significantly lower in patients randomized to liraglutide; emerging evidence indicates that hypoglycemia may be more harmful in patients with existing CV disease, so less hypoglycemia could help explain the CV mortality reduction in the LEADER trial. Other direct vascular or cardiac effects of GLP-1 receptor agonists have been proposed and could have contributed to the CV benefits seen (40).

Taken together and accepting the caveats mentioned in the previous text, the somewhat different pattern of CV benefits in the LEADER versus SUSTAIN-6 trials (**Figures 1A and 1B**) suggests that a class effect of GLP-1 receptor agonists on CV outcomes cannot be assumed; rather, benefits and potential harms may differ between different GLP-1 receptor agonists. The results of EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial), testing once-weekly exenatide, are eagerly awaited (41). It should also be noted that the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) CVOT did not reduce MACE in T2D patients following acute coronary syndrome (42), but whether these results were due to the short-acting nature of lixisenatide compared with other GLP-1 agonists requires further research.
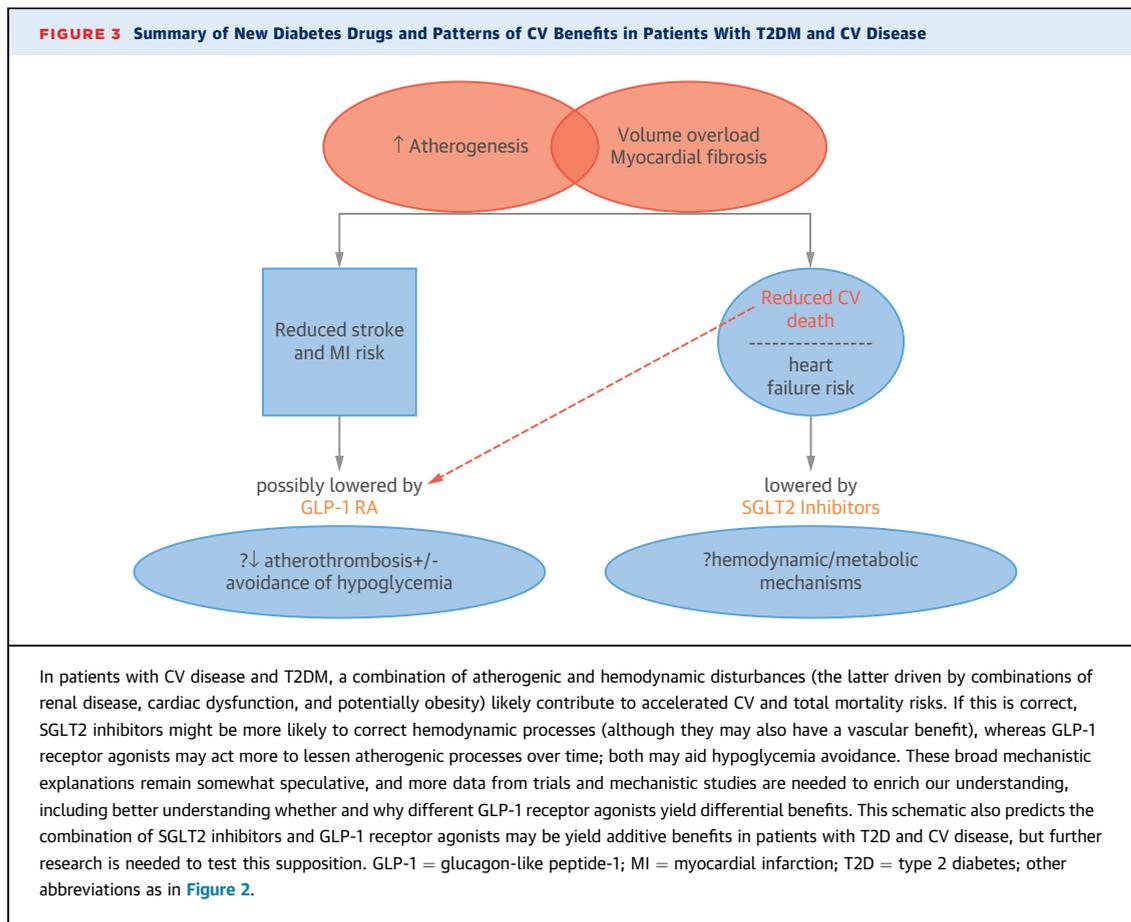
As with the SGLT2 inhibitors, a good understanding of the potential side effects of GLP-1 receptor agonists should be known. In trials of these agents, more patients discontinued liraglutide or semaglutide than placebo due to adverse events. This was primarily due to gastrointestinal adverse effects, a known side effect of GLP-1 receptor agonist drugs. There was a slight numerical excess of retinopathy events with liraglutide versus placebo (0.6 vs. 0.5 per 100 patient years); rates of retinopathy events were higher in those treated with semaglutide (HR: 1.76; 95% CI: 1.11 to 2.78), which is a concern, although the number of events is rather small. The more rapid glucose reduction seen with semaglutide is theorized to explain increased retinopathy, but more work is needed to confirm the findings and, if confirmed, examine the mechanisms. There was a concern before the trial that GLP-1 receptor agonists might increase pancreatic conditions, but these concerns were not realized.

BROADER LESSONS LEARNED FROM RECENT AND PRIOR CVOTs OF DRUGS FOR DIABETES

Diabetes is associated with a higher rates of incident CV disease, which most have thought to be due to excess atherothrombotic risk, with hyperglycemia adding fire to a background of hypertension, dyslipidemia, and obesity. However, as MI and stroke rates have declined substantially (43), due in considerable part to much better treatments with statins and antihypertensive agents, heart failure and peripheral arterial disease have become the 2 commonest first presentations of CV disease in those with T2D (44). Moreover, once patients with T2D develop CV disease, their risk of premature mortality escalates (45), and it is here that the unexpected and rapid CV mortality and heart failure benefits in the EMPA-REG OUTCOME trial have emerged. These benefits support greater roles of cardiac structural abnormalities and excess fluid loads in driving premature death in such patients. Parallel improvements in renal outcomes, CV death, and heart failure hospitalization also emphasize the importance of cardio-renal interactions in patients with T2D and CV disease. Although cardiologists appreciate the role of kidney dysfunction in heart failure (46), a recalibration toward appreciating overlapping mechanisms with the heart, kidney, and T2D is worthwhile.

The recent positive CVOTs have also taught all clinicians that it is not necessarily lowering glucose per se (or even how much one lowers glucose) that dictates net CVD effects of diabetes drugs. Rather, the mechanism by which any particular diabetes drug works and its associated multiple effects on other pathways may matter as much (if not more) to observed CVD benefits. The EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 trials have shown that blood glucose and CV and total mortality can be lowered in parallel with specific drugs that might improve the hemodynamic status of patients or lower glucose in conjunction with reduced weight, lower risk for hypoglycemia, and improved blood pressure; possible

FIGURE 3 Summary of New Diabetes Drugs and Patterns of CV Benefits in Patients With T2DM and CV Disease

In patients with CV disease and T2DM, a combination of atherogenic and hemodynamic disturbances (the latter driven by combinations of renal disease, cardiac dysfunction, and potentially obesity) likely contribute to accelerated CV and total mortality risks. If this is correct, SGLT2 inhibitors might be more likely to correct hemodynamic processes (although they may also have a vascular benefit), whereas GLP-1 receptor agonists may act more to lessen atherogenic processes over time; both may aid hypoglycemia avoidance. These broad mechanistic explanations remain somewhat speculative, and more data from trials and mechanistic studies are needed to enrich our understanding, including better understanding whether and why different GLP-1 receptor agonists yield differential benefits. This schematic also predicts the combination of SGLT2 inhibitors and GLP-1 receptor agonists may be yield additive benefits in patients with T2D and CV disease, but further research is needed to test this supposition. GLP-1 = glucagon-like peptide-1; MI = myocardial infarction; T2D = type 2 diabetes; other abbreviations as in **Figure 2**.

beneficial direct effects on atherosclerosis may also be considered (**Figure 3**).

CLINICAL IMPLICATIONS FOR THE PRACTICING CARDIOLOGIST

It is impossible for cardiologists to assume full responsibility for blood glucose management; however, a change in thinking regarding initiation and titration of therapies with CV benefits is necessary, particularly because most patients with T2D develop CV disease and are frequently encountered in cardiology practice. As well, the patient with CV disease frequently has unrecognized or undertreated T2D; in the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) study, in addition to the 27% of patients with recognized T2D, 11% of patients with heart failure had unrecognized T2D (47).

In light of the new trial evidence of clinical benefit over and above existing therapies, and with the emergence of recent guidelines mentioning these CV benefits (48,49), it seems logical to suggest that cardiologists perform routine, systematic measurement

of HbA_{1c} in all patients with established CV disease (**Central Illustration**). Measurement of HbA_{1c} should be performed both to diagnose T2D and to identify those who would have met the inclusion criteria for the positive CVOTs (e.g., HbA_{1c} 7% to 10% in EMPA-REG OUTCOME, and >7% in the LEADER and SUSTAIN trials). Care of patients with T2D and CV disease should involve strong consideration for use of glucose-lowering drugs that improve CV outcomes over and above existing therapies, and not solely on the glucose-lowering abilities of therapies. In this regard, beyond their glucose-lowering effects, empagliflozin, liraglutide, or semaglutide (when available) might be considered for eligible patients for their proven CV benefits. Of course, identifying new diabetes in patients with CV disease will also have other beneficial implications, including, where relevant, the choice of revascularization (coronary artery bypass graft vs. percutaneous coronary intervention) and the aggressiveness of management of other risk factors.

In analogy to the "heart team" approach used for those with other forms of heart disease, collaboration among cardiologists, primary care physicians, and

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CENTRAL ILLUSTRATION Novel Paradigm for Care of the Patient With CV Disease and T2DM

Patient with established cardiovascular (CV) disease but <u>no prior</u> Type 2 diabetes mellitus (T2DM): Cardiologist to perform routine, systematic measurement of HbA1c to evaluate presence of T2DM

And/or

Eligible patients with CV disease <u>and prior</u> T2DM

Consider recommending treatments if no contraindication:

SGLT2 inhibitor: empagliflozin

Decreased CV mortality and decreased heart failure hospitalizations

+ Decreased blood glucose

+ Promotes weight loss

+ Renal benefits

(or)

GLP-1 receptor agonist: liraglutide

Decreased CV mortality

+ Decreased blood glucose

+ Promotes weight loss

+ Potential renal benefits

Refer to primary care physician or endocrinologist

Follow CV and T2DM progress in tandem

Sattar, N. et al. J Am Coll Cardiol. 2017;69(21):2646–56.

The cardiologist will need to take a more active role in patient care by more frequent testing for T2DM using HbA$_{1c}$ in patients with CV disease to identify suitable patients for newer T2DM therapies. Cardiologists should also prescribe T2DM drugs with proven CV benefits, and work more efficiently with diabetologists and primary care physicians to manage their patients. CV = cardiovascular; GLP = glucagon-like peptide; HbA$_{1c}$ = glycosylated hemoglobin; SGLT = sodium-glucose cotransporter; T2DM = type 2 diabetes mellitus.

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diabetologists will be necessary to achieve the goal of more widespread treatment of vulnerable patients with T2D. Management of adverse effects, such as genital infections, are an obvious example of where this approach is likely to be beneficial. There is no reason that cardiologists cannot initiate SGLT2 inhibitors, with the patient then monitored by colleagues in primary care or diabetology. Although cardiologists might recommend GLP-1 receptor agonists, specialized teaching by primary care physicians and/or diabetologists might be needed. If CV specialists do not feel comfortable prescribing these drugs, they should inform not only the patients, but also the primary care physician (and other health care professionals involved in the patient's care) of the potential benefits of adding these drugs.

CLINICAL IMPLICATIONS FOR THE PRACTICING DIABETES SPECIALIST

Diabetologists have lowered CV risk by prescribing statins and antihypertensive agents for decades.

Based on present data, if a diabetes specialist recognizes that a patient has CV disease, he or she has identified a patient who might benefit from therapy with newer agents, such as SGLT2 inhibitors or GLP-1 receptor agonists. Although numerous therapies exist to lower blood glucose, it will take a continued shift in philosophy toward using therapies that not only lower blood glucose modestly, but also significantly reduce CV risk. Our view is that, given that empagliflozin is oral (rather than injectable) with an apparently robust effect on CVD and total mortality, it would likely be the preferred choice after metformin in most patients with CVD and diabetes. Of course, treatments need to be individualized, and other factors, such as poor renal function and patient preference, may make a GLP-1 receptor agonist the preferable choice in some patients.

THE FUTURE

There is an array of ongoing safety CV outcome trials with DPP-4 inhibitors, GLP-1 receptor agonists, and

SGLT2 inhibitors with study groups similar to those in the trials described in this paper, but also, importantly, including patients without CVD (50). The knowledge of the pros and cons of other agents in varying populations will evolve over the next 1 to 5 years. Trials with SGLT2 inhibitors are also underway in patients with heart failure, including those with T2D or pre-diabetes, as well as those without T2D. Trials of SGLT2 inhibitors in patients with chronic kidney disease are also underway. Trials of the combined effect of SGLT2 inhibitors and GLP-1 receptor agonists may also be reasonable, given the possible (and potentially additive) differences in mechanism of benefit of these agents.

Ultimately, studies of newer drugs for T2D must shift to focus on patients without prevalent CV disease (50). It is typically harder to prove CV benefit in such trials, given lower rates of incident events; enrichment of patient populations with tools to identify higher risk for CV events might be a way that can identify subgroups that potentially benefit. Circulating biomarkers might be such a tool. When measured in patients with T2D, concentrations of N-terminal pro–B-type natriuretic peptide and high-sensitivity troponin may be helpful to predict future CV events, including heart failure and atherothrombotic events (51-53). Thus, it may be possible to envision a strategy of biomarker-guided screening and treatment of patients with T2D who are at high risk for CV events.

CONCLUSIONS

When the first few CVOTs of newer diabetes drugs began to report CV safety without reduction in CV risk, some started to question the value of these clinical trials. However, recent CVOTs have shown convincing evidence of CV benefit with an SGLT2 inhibitor and 2 classes of GLP-1 receptor agonists. Cardiologists should take note of the substantial reduction in CV events and CV mortality in these trials. If clinical experience follows the results of studies such as EMPA-REG OUTCOME (SGLT2 inhibitor) or LEADER (GLP-1 receptor agonist), a sizeable proportion of patients seen and managed by cardiologists on a daily basis might benefit from treatment with these novel agents. Consequently, cardiologists would do well to familiarize themselves with these drug classes, as many of their patients (i.e., T2D plus CV disease) stand to benefit from their use. Cardiologists should also consider screening more widely for T2D, to identify patients who could benefit sooner from such drugs. By doing so, it will be possible to better influence the rising burden of patients with both T2D and CV disease.

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