JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 69, NO. 21, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.04.014

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)

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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Manuscript received December 21, 2016; revised manuscript received April 3, 2017, accepted April 3, 2017.

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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

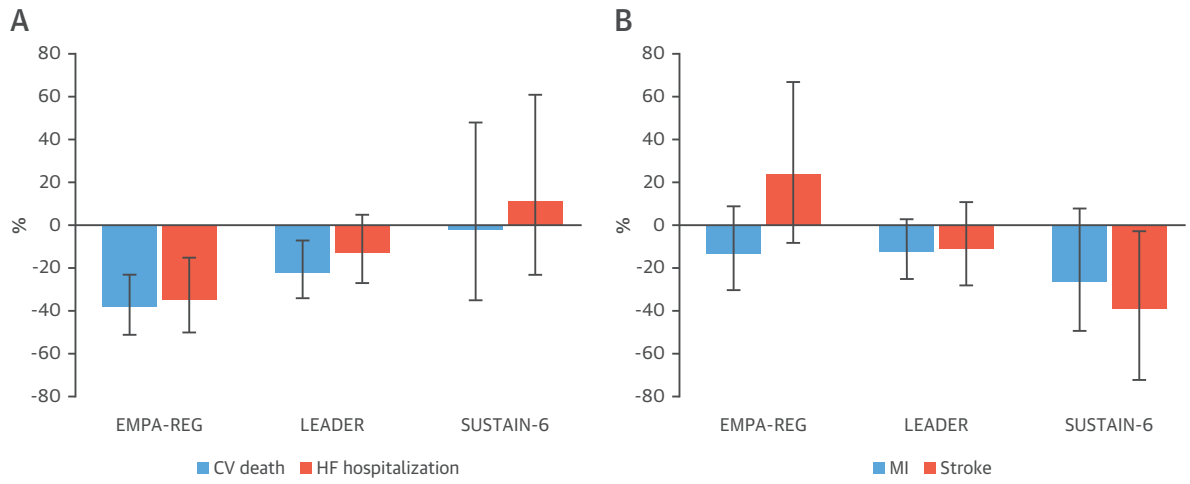
Although numerous therapies for T2D have been associated with an increased risk of CV events, 3 recent CVOTs have shown benefit in terms of hard clinical endpoints (Table 1) (2–4). We first review the results for the sodium-glucose cotransporter (SGLT) 2 inhibitor, empagliflozin, before discussing results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

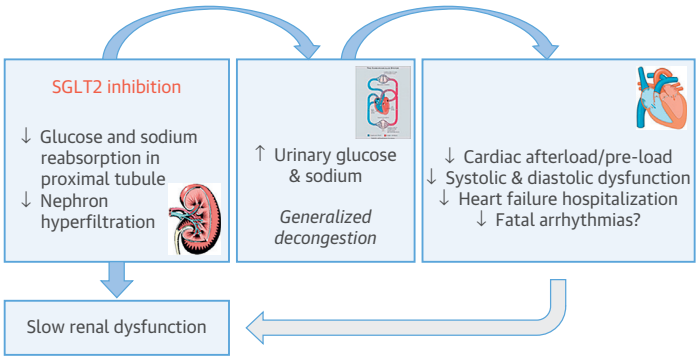
established CV disease, and randomized them to placebo, empagliflozin 10 mg, or empagliflozin 25 mg. All study participants had established CV disease. The primary endpoint of EMPA-REG OUTCOME was 3-point MACE (CV mortality, nonfatal MI, and nonfatal stroke). Patients randomized to empagliflozin had 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



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

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