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REVIEW

Closing the knowledge gap on cardiovascular disease in type 2 diabetes: the EMPA-REG OUTCOME trial and beyond

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Abstract

Type 2 diabetes mellitus (T2DM) is associated with marked cardiovascular (CV) morbidity and mortality, including heart failure (HF). Until recently, an oral glucose-lowering agent that improved hyperglycemia as well as provided CV benefits in patients with T2DM and cardiovascular disease (CVD) was lacking. The newest class of glucose-lowering agents, sodium glucose cotransporter 2 (SGLT2) inhibitors, includes canagliflozin, dapagliflozin, and empagliflozin. Prior to the release of the LEADER trial results, the recent EMPA-REG OUTCOME study was the only dedicated CV trial to demonstrate a reduction in major adverse cardiac events, CV mortality, and all-cause mortality and a reduction in hospitalization for HF with empagliflozin, given on top of standard-of-care therapy in patients with T2DM and CVD. This paper summarizes the results from EMPA-REG OUTCOME and discusses their significance and clinical implications.

Keywords: sodium glucose cotransporter 2 inhibitor, type 2 diabetes mellitus, empagliflozin, cardiovascular disease, heart failure, glucose-lowering, major adverse cardiovascular events.

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; AE, adverse event; ARB, angiotensin receptor blocker; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events; MI, myocardial infarction; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT2, sodium glucose cotransporter 2; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; UTI, urinary tract infection.

Citation

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"The gap between what we know and what we aim for persists. And this gap complicates everything we do."

Atul Gawande, *Complications: A Surgeon's Notes on an Imperfect Science*

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic health conditions in the United States: approximately 15% of adults have diabetes, with nearly one-third being undiagnosed [1]. Until the late 1990s, physicians in the United States had access to only insulin and sulfonylureas (SUs)—both drugs that are effective in lowering glucose levels but associated with hypoglycemia and weight gain [2]. T2DM is associated with substantial cardiovascular (CV) morbidity and mortality [3]. Heart failure (HF) is a frequent comorbid condition associated with poor prognosis in diabetes, particularly among older patients [3,4]. As new drugs for T2DM have been introduced, cardiac safety has emerged as an important milestone requested by the US Food and Drug Administration (FDA), owing in part to the emerging heart-disease risk associated with peroxisome proliferator–activated receptor agonists (i.e., thiazolidinediones [TZDs], dual agonists [muraglitazar]) in the mid 2000s [5,6]. Since 2008, the FDA has required demonstration of CV safety for all glucose-lowering drugs [7]. In addition, management of concomitant HF in T2DM is particularly challenging, as some glucose-lowering agents, such as TZDs, are contraindicated in patients with HF [8]. Until recently, there was an unmet need for an oral agent that improved glycemia as well as provided CV benefits, including decreasing HF in patients with, or at risk of, cardiovascular disease (CVD). The EMPA-REG OUTCOME trial

was the first dedicated CV study to demonstrate a reduction in major adverse cardiac events (MACE), CV mortality, and hospitalization for HF with a glucose-lowering agent, the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin, given on top of standard-of-care therapy for T2DM and CVD.

The SGLT2 inhibitors reduce glucose reabsorption in the proximal convoluted tubule, which leads to glucosuria and reduces hyperglycemia in individuals with T2DM [9]. Clinical trials demonstrate that SGLT2 inhibitors reduce glycated hemoglobin (HbA1c), lower systolic blood pressure (SBP), and decrease body weight [10–12]. These agents are associated with a low risk of hypoglycemia except when used with insulin or insulin secretagogues [13–15]. In current treatment algorithms from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), SGLT2 inhibitors are an option for first-line therapy if metformin is not tolerated or contraindicated [2,16]. This class is also a preferred treatment option for combination with metformin (or other agents) as a second- or third-line therapy [2,16].

Summary of Zinman et al. [17] and Fitchett et al. [18]

Methods

The EMPA-REG OUTCOME study was a randomized, double-blind, placebo-controlled trial designed to assess the effects of empagliflozin (once daily, 10 or 25 mg) compared with placebo on CV events in patients with T2DM and at high CV risk receiving a standard-of-care therapy [19]. Eligible patients had T2DM (HbA1c, 7.0–9.0% if drug naive and 7.0–10.0% if receiving stable glucose-lowering therapy), a body mass index ≤45 kg/m^2, established CVD, and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 [17]. Patients who had had investigator-reported HF at baseline were permitted to participate in the trial; no restrictions regarding New York Heart Association (NYHA) class or ejection fraction were implied [18].

The purpose of the EMPA-REG OUTCOME study was not to assess whether empagliflozin is efficacious in lowering glucose, which has been demonstrated elsewhere [10]. Nor was it designed to assess the effect of lowering glucose per se on CV events; instead, the aim was to assess the effect of empagliflozin on CV events; hence glucose control was to be optimized in both arms of the study. Patients entered a 2-week, open-label, placebo run-in period where background glucose-lowering therapy was unchanged to assess their ability to adhere to trial procedures [17,19]. Those still qualifying were then randomized (1:1:1) to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily. Background glucose-lowering therapy was kept unchanged for the first 12 weeks, but intensification was permitted if the confirmed fasting plasma glucose (FPG) was >240 mg/dL. Treatment of CV risk factors (e.g., hypertension, dyslipidemia) was encouraged according to the best standard of care consistent with local guidelines.

The primary outcome was a composite of death from CV causes, non-fatal myocardial infarction (MI; excluding silent MI), or non-fatal stroke [17,19]. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina. The primary hypothesis was noninferiority for the primary outcome with the pooled doses of empagliflozin (10 and 25 mg) compared with placebo with a margin of 1.3 for the hazard ratio (HR). The trial continued until an adjudicated primary-outcome event had occurred in ≥691 patients [17]. Other prespecified outcomes included CV death, non-fatal MI, non-fatal stroke, hospitalization for HF, and all-cause mortality.

Safety was assessed by monitoring adverse events (AEs); AEs of special interest included confirmed hypoglycemic AEs, and AEs consistent with urinary tract infections (UTIs), AEs consistent with genital mycotic infections, as well as volume depletion, acute renal failure, bone fractures, diabetic ketoacidosis (DKA), and thromboembolic events.

Baseline characteristics

Baseline characteristics were well balanced between groups [17,19]. Most patients were male (72%), white (72%), and from European countries (41%) [19]. Mean HbA1c was 8.1%, mean body weight was 86 kg, mean SBP and diastolic blood pressure (DBP) were 136 and 77 mmHg, respectively, and mean eGFR was 74 mL/min/1.73 m^2. Patients were older (mean age, 63 years), had a long duration of T2DM (>10 years, 57%), and the majority had established CVD (coronary artery disease, 76%; history of MI, 47%; history of stroke, 23%; HF, 10%). All but 2% of patients were receiving other glucose-lowering agents (metformin, 74%; insulin, 48%; SUs, 43%). Ninety-five percent of patients were receiving antihypertensive therapy (e.g., angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARBs], 81%; β-blockers, 65%; diuretics, 43%), approximately 80% were receiving lipid-lowering therapy (e.g., statins, 77%), and nearly 90% were receiving antiplatelet therapy (e.g., aspirin, 81%).

Primary and secondary outcomes

A total of 7020 patients were treated and included in the primary analysis [17]. In the overall population, the median treatment duration was 2.6 years, and the median observation period was 3.1 years. The primary MACE outcome of CV death, non-fatal MI, and non-fatal stroke occurred in 10.5% of patients on empagliflozin (pooled 10 and 25 mg groups) and in 12.1% of patients on placebo (relative risk reduction, 14%; Table 1). The results for the individual doses of empagliflozin were in the same direction and extent as the pooled analysis for the primary composite outcome (empagliflozin 10 mg; HR, 0.85; 95% confidence interval [CI], 0.72–1.01; p=0.07; and empagliflozin

Table 1. Efficacy outcomes from EMPA-REG OUTCOME [17,18].

CV outcome	Placebo (N=2333) n (%)	Empagliflozin[a] (N=4687) n (%)	Hazard ratio (95% CI)	*p*-value
Three-point MACE[b]	282 (12.1)	490 (10.5)	0.86 (0.74–0.99)	<0.001[c] 0.04[d]
Four-point MACE[e]	333 (14.3)	599 (12.8)	0.89 (0.78–1.01)	<0.001[c] 0.08[d]
All-cause mortality	194 (8.3)	269 (5.7)	0.68 (0.57–0.82)	<0.001
CV death	137 (5.9)	172 (3.7)	0.62 (0.49–0.77)	<0.001
Non-fatal MI[f]	121 (5.2)	213 (4.5)	0.87 (0.7–1.09)	0.22
Non-fatal stroke	60 (2.6)	150 (3.2)	1.24 (0.92–1.67)	0.16
Hospitalization for HF	95 (4.1)	126 (2.7)	0.65 (0.50–0.85)	0.002
Hospitalization for HF or CV death	198 (8.5)	265 (5.7)	0.66 (0.55–0.79)	<0.001
Hospitalization for or death from HF	104 (4.5)	129 (2.8)	0.61 (0.47–0.79)	<0.001

CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction.
[a]Pooled analysis of empagliflozin 10 and 25 mg.
[b]Death from CV causes, non-fatal MI, or non-fatal stroke: primary outcome.
[c]For noninferiority.
[d]For superiority.
[e]Death from CV causes, non-fatal MI, or non-fatal stroke, or hospitalization for HF: secondary outcome.
[f]Excluding silent MI.

25 mg; HR, 0.86; 95% CI, 0.73–1.02; p=0.09) but were not significant owing to the smaller number of events per group.

No significant decrease was observed in the relative risk of stroke or non-fatal MI with empagliflozin (Table 1); thus the MACE risk reduction was driven primarily by a significant 38% relative risk reduction in CV death. Of note, empagliflozin treatment resulted in a significant 32% relative risk reduction in all-cause mortality. In addition, empagliflozin treatment resulted in small decreases from baseline in body weight (approximately 2 kg) and waist circumference (approximately 2 cm) when compared with placebo [20]. Reductions in uric acid levels and in SBP and DBP, without increase in heart rate, were observed. Treatment with empagliflozin was associated with increases in both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). To give an idea of the size of the changes, at 164 weeks, mean LDL-C values in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups were approximately 87.5, 88.0, and 89.0 mg/dL, respectively; although it should be noted that about one-fourth of patients had lipid-lowering drugs (mostly statins) introduced after the study start, and investigators were encouraged to treat all CV risk factors to the best possible standard of care.

Subgroup analysis

Analysis of the primary outcome in various subgroups was prespecified by the study protocol, and after the initial results were available, analyses of death from CV causes were conducted post hoc [17]. For the primary outcome, some subgroups, such as patients aged ≥65 years and those with baseline HbA1c <8.5%, appeared to show better responses [17]. However, the subgroup statistical analysis was not corrected for multiplicity, which limits the validity of these findings. Looking at the outcome of CV death, there was no heterogeneity between groups, that is, a consistent benefit across all subgroups [17]. In some subgroups, confidence intervals were wide, reflecting relatively low numbers of patients in those groups, for example, those with only peripheral vascular disease at baseline and those not on antihypertensive therapy. As in most multinational studies for T2DM therapies, "black/African American" patients were relatively underrepresented in the study (making up only 5% of the study population). Although subgroup analysis by race showed no heterogeneity, generalizing the results of EMPA-REG OUTCOME to black/African Americans is somewhat limited by the relatively small number of patients.

Heart failure results

A further analysis of EMPA-REG OUTCOME data focused on HF outcomes in all patients and in subgroups, including those with and without HF at baseline [18]. Hospitalization for HF was defined as an event that required inpatient admission or a 12-hour stay in an emergency department resulting from clinical manifestation of new or worsening HF. This analysis demonstrated a 34% relative risk reduction in the composite

outcome of hospitalization for HF or CV death, a 39% relative risk reduction in hospitalization for HF or death from HF, and a 35% relative risk reduction in hospitalization for HF with empagliflozin treatment compared with placebo added on top of a standard-of-care therapy (Table 1). No difference in the reduction of these risks was observed based on the presence of HF at baseline. There was no difference in hospitalization for HF based on age, gender, eGFR, insulin use, or use of other baseline medications (e.g., ACE inhibitors/ARBs, diuretics, β-blockers, mineralocorticoid receptor agonists).

Safety findings

The safety profile of empagliflozin was consistent with the known mechanism of SGLT2 inhibition, and there were no unexpected AEs. The percentage of patients who had AEs, serious AEs, and AEs leading to discontinuation of study drug were similar with empagliflozin and placebo. Likewise, the percentage of patients with confirmed hypoglycemic events, venous thromboembolic events, bone fractures, acute renal failure, DKA, and events consistent with volume depletion was similar between the two groups. UTIs were reported in similar proportions of patients in the empagliflozin and placebo groups, and in both study arms the rate was higher in women than men (Table 2). Urosepsis was rare but reported more often in patients in the empagliflozin group (0.4 vs 0.1% of those in the placebo group). Genital infections were reported in more patients in the pooled empagliflozin group (6.4%) than in the placebo group (1.8%) (Table 2).

Table 2. Adverse events reported in EMPA-REG OUTCOME [17].

	Placebo (N=2333) n (%)	Empagliflozin[a] (N=4687) n (%)
Events consistent with UTIs	423 (18.1)	842 (18.0)
Men	158 (9.4)	350 (10.5)
Women	265 (40.6)	492 (36.4)[b]
Complicated UTIs[c]	41 (1.8)	82 (1.7)
Events consistent with genital infections	42 (1.8)	301 (6.4)[d]
Men	25 (1.5)	166 (5.0)[d]
Women	17 (2.6)	135 (10.0)[d]
Events consistent with volume depletion	115 (4.9)	239 (5.1)
Diabetic ketoacidosis	1 (<0.1)	4 (0.1)
Acute renal failure	166 (6.6)	246 (5.2)[e]
Any confirmed hypoglycemic AE	650 (27.9)	1303 (27.8)
Hypoglycemic event requiring assistance	36 (1.5)	63 (1.3)
Thromboembolic events	20 (0.9)	30 (0.6)
Bone fractures	91 (3.9)	179 (3.8)

AE, adverse event; UTI, urinary tract infection.
[a]Pooled analysis of empagliflozin 10 and 25 mg.
[b]$p<0.05$ compared with placebo.
[c]Defined as pyelonephritis, urosepsis, or a serious AE consistent with UTI.
[d]$p<0.001$ compared with placebo.
[e]$p<0.01$ compared with placebo.

These findings are consistent with recent evidence from a predefined pooled analyses of data from 17 randomized, Phase I–III trials comparing patients who received placebo (n=3695), empagliflozin 10 mg (n=3806), or empagliflozin 25 mg (n=4782) [21]. In this analysis, the incidence of events consistent with UTIs, decreased renal function, DKA, venous thromboembolic events, and hepatic injury was low and similar across all treatment groups. However, it has previously been noted that in some individual studies, UTI is reported more frequently with empagliflozin than with placebo, and patients should be advised to seek treatment if they do experience symptoms of UTI, as the infection may become serious [14]. In the pooled analysis, as in EMPA-REG OUTCOME, the incidence of genital infection was higher in patients treated with empagliflozin than placebo; genital infections are typically associated with SGLT2 inhibitor treatment [21]. The incidence of AEs consistent with volume depletion was similar with placebo, empagliflozin 10 mg, and empagliflozin 25 mg (1.6, 1.5, and 1.3/100 patient-years, respectively) and was higher with empagliflozin 25 mg than placebo or empagliflozin 10 mg in patients who were older than 75 years. The incidence of hypoglycemia with empagliflozin was increased only when used in combination with an SU and/or basal insulin [21].

Significance and practical implications

Patient selection

Patients in the EMPA-REG OUTCOME study compare well with patients seen in everyday clinical practice for the treatment of T2DM; specifically patients with high risk of CVD who are receiving multiple medications for T2DM and other comorbidities were included. Patients were older (mean age, 63 years), had a long duration of T2DM (>10 years, 57%), were receiving dual glucose-lowering therapy (nearly 50%), and were receiving insulin (nearly 50%). Overall, 99% of patients had established CVD and were well treated with approximately 80% receiving renin-angiotensin-aldosterone system (RAAS) blockers, 81% also receiving lipid-lowering therapies, and nearly 90% receiving antiplatelet therapy [19].

These results are noteworthy given that empagliflozin was administered on top of a standard-of-care therapy that was

more advanced than in earlier landmark trials demonstrating mortality benefits in high-CV-risk populations. For example, in the Scandinavian Simvastatin Survival Study (4S) [22], mortality benefits were observed with simvastatin although patients had fewer comorbidities (T2DM, 5%; hypertension, 26%) and were not yet receiving the protection from ACE inhibitor/ARB therapy that was afforded to patients in the EMPA-REG OUTCOME trial. By the time the HOPE/MICRO-HOPE study [23] was conducted, statin use had increased but not to the levels observed in the EMPA-REG OUTCOME trial. That study demonstrated a mortality benefit with ramipril in patients with T2DM and high CV risk and ushered in the ACE inhibitor era. In HOPE/MICRO-HOPE, 22% of patients were taking hypolipidemic agents, whereas in EMPA-REG OUTCOME, 80% were receiving lipid-lowering therapy, primarily with a statin. Moreover, in HOPE/MICRO-HOPE, the proportion of patients receiving other CV therapies was lower than the proportion of patients receiving such therapies in EMPA-REG OUTCOME (β-blockers, 28 vs 65%; diuretics, 20 vs 43%; or aspirin, 55 vs 83%).

One limitation of EMPA-REG OUTCOME is that only patients at high CV risk were included in the study—a significant limitation given that many patients with T2DM do not have a history of CVD. Future studies are planned in patients with a history of HF, but these patients are also at high risk, and results are not anticipated for some time [24]. The only studies conducted in these patients have been in shorter-term trials looking at HbA1c as the endpoint, rather than at CV events. A meta-analysis of CV events in patients at low/medium risk in shorter-term trials has been performed, but the number of CV events was too low to draw meaningful conclusions (32 events in 2770 in the empagliflozin group [1.2%] and 25 in 1502 in the placebo group [1.7%]) [25].

Heart failure

Treatment of HF in T2DM remains a challenge due to a lack of clear guidelines and a paucity of evidence regarding the safety and efficacy of T2DM treatments in this population [18]. The risk of death from HF remains substantial in diabetes [26]. Results from five other prospective, placebo-controlled CV outcome trials in patients with diabetes and at high risk of CV events have been completed in addition to EMPA-REG OUTCOME and have not shown improvement in HF outcomes [27–30], three trials with dipeptidyl peptidase-4 (DPP-4) inhibitors (saxagliptin, alogliptin, and sitagliptin) [28–30] and two trials with glucagon-like peptide (GLP)-1 receptor agonists (lixisenatide and liraglutide) [27,31].

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial infarction (SAVOR-TIMI 53) trial included 16,492 patients with T2DM with a history of CVD or at high risk of CV events and followed them for a median of 2.1 years [32]. The Examination of Cardiovascular Outcomes with Alogliptin versus standard of care (EXAMINE) study included 5380 patients with T2DM with acute coronary syndrome (ACS; acute MI or unstable angina requiring hospitalization) within the previous 15–90 days and followed them for a median of 18 months [29]. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized 14,671 patients to sitagliptin or placebo and followed them for a median of 3 years [30]. Finally, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial included 6068 patients with T2DM and a recent ACS event who were followed for a median of 25 months [27]. All four trials of incretin therapies demonstrated noninferiority for the primary composite MACE endpoint (SAVOR-TIMI and EXAMINE: three-point MACE; TECOS and ELIXA: four-point MACE [included hospitalization for unstable angina]), showing neither an increase nor a decrease in the risk of major CV events. However, the SAVOR-TIMI trial showed an unexpected increase in the risk of hospitalization for HF (HR, 1.27; 95% CI, 1.07–1.51; p=0.007); post hoc analyses determined that this increased risk was highest in patients with elevated levels of natriuretic peptides, prior HF, or chronic kidney disease [32]. Follow-up analyses from EXAMINE revealed a non-significant trend toward increased risk of HF outcomes with alogliptin [33]. The label information for saxagliptin [34] and alogliptin [35] both contain a warning regarding HF risk. In TECOS, sitagliptin was noninferior to placebo for the primary MACE outcome, and rates of hospitalization for HF did not differ between the sitagliptin and the placebo groups [30]. Similarly, in the ELIXA trial, the rates for hospitalization for HF were similar for lixisenatide (4.0%) and placebo (4.2%; HR, 0.96; 95% CI, 0.75–1.23) [27]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [31], which assessed the effects of the glucagon-like peptide-1 (GLP-1) agonist liraglutide on CV outcomes in patients with T2DM and high CV risk, was the second trial—after EMPA-REG OUTCOME—to demonstrate significant benefit in reducing the risk of the primary MACE outcome. After a median follow-up of 3.9 years, the relative risk of experiencing a MACE event was reduced by 13% with liraglutide (HR, 0.87; 95% CI, 0.78–0.97; p<0.001 for noninferiority; p=0.01 for superiority). For hospitalization for HF, there were numerically fewer events in the liraglutide group than in the placebo group; however, the reduction did not meet statistical significance (HR, 0.87; 95% CI, 0.73–1.05; p=0.14) [31].

Mechanism of action for observed benefits

While EMPA-REG OUTCOME was not designed to elucidate the mechanism of action of empagliflozin responsible for the observed CV benefits, multiple pathways have been proposed. In a series of commentaries following the publication of the EMPA-REG OUTCOME study [36–40], it was speculated that empagliflozin might have additive cardioprotective effects via activation of non-classic RAAS pathways, supported by the fact that 81% of patients in this study were receiving ACE inhibitors or ARBs [38]. Others speculated that the volume status of patients is vital in HF and that empagliflozin might

represent a new type of osmotic diuretic with CV effects not previously observed with other agents [40]. For example, in the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) study, rosiglitazone was associated with volume expansion, a 2–3% decrease in hematocrit, and an increase in the risk of HF [41], whereas empagliflozin was associated with volume contraction, a 4.8% increase in hematocrit [37], and a 35% relative reduction in the risk of hospitalization for HF [17]. Although some researchers have speculated that glucagon plays an important role in modulating cardiac function [36], others counter that an increase in glucagon was unlikely to contribute to reduced CV mortality or hospitalization for HF in the EMPA-REG OUTCOME study, because in animal models, it has been shown that glucagon-receptor activation had a detrimental effect on myocardial function [42,43]. Furthermore, glucagon infusion into humans has not demonstrated any effect on left ventricular function [43,44]. The temporal association between the rapid reduction of CV events in the empagliflozin-treated groups (within 2–4 months) and decreases in blood pressure and intravascular volume favors a hemodynamic mechanism of action [37]. The lack of effect of empagliflozin on the rates of non-fatal MI or non-fatal stroke, taken together with the short time it took for the Kaplan–Meier curves to separate, likely indicates that the effects are not mediated via atherosclerotic pathways; in other CV therapy trials, differences between groups tended to take years, not months, to materialize [22,23]. More recently, it has been proposed that the effect of empagliflozin on fatty acid metabolism may have a beneficial effect via production of ß-hydroxybutyrate, an efficient fuel for the heart [45] as well as for the kidney [46]. This potential mechanism could work in tandem with volume contraction and is not exclusive of other mechanisms of benefit, and indeed it seems likely that the mechanism for the reduction in risk of CV events and of death from any cause is multifactorial. Other CV risk factors known to be affected by SGLT2 inhibition, such as blood pressure, weight, visceral adiposity, hyperinsulinemia, as well as changes in arterial stiffness, albuminuria, uric acid levels, and oxidative stress are discussed in detail by Inzucchi et al [47]. Furthermore, the postulated roles of these mechanisms in the benefits observed with empagliflozin are discussed by Abdul-Ghani et al [43].

Renal outcomes

Chronic kidney disease is common in people with diabetes; in the United States, more than 30% of adults with diabetes also have kidney disease, and those with kidney disease as well as diabetes are at increased risk of premature mortality [48]. Preventing development or progression of kidney disease in patients with T2DM is thus a key concern and was a prespecified analysis of EMPA-REG OUTCOME. As discussed above, EMPA-REG OUTCOME included patients with eGFR ≥30 mL/min/1.73 m^2 at screening; patients with more severe renal impairment were not eligible to participate [49]. The majority of patients had eGFR ≥60 mL/min/1.73 m^2, 17.8% had eGFR 45 to <60 mL/min/1.73 m^2, and 7.7% had eGFR ≥30 to <45 mL/min/1.73 m^2. At baseline, 80.7% of the patients were receiving ACE inhibitors or ARBs. Over the course of the study, patients receiving empagliflozin (on top of a standard-of-care therapy) had a significantly reduced risk of new or worsening nephropathy relative to the placebo group (HR, 0.61; 95% CI, 0.53–0.70; $p<0.001$) [49]. In addition, treatment with empagliflozin resulted in a significant 46% relative-risk reduction in the composite renal endpoint of doubling of creatinine and eGFR <45 mL/min/1.73 m^2, initiation of renal replacement therapy, and death due to renal disease (HR, 0.54; 95% CI, 0.40–0.75; $p<0.001$) [50]. Looking at the change in eGFR over time, the empagliflozin group had an initial drop in eGFR after starting treatment, but renal function stabilized over time while eGFR in the placebo group followed the natural decline. Furthermore, after stopping treatment, patients on both empagliflozin doses had an increase in eGFR to baseline levels, not seen in the placebo group, giving final differences between empagliflozin and placebo of 4.7 mL/min/1.73 m^2 ($p<0.001$). The reasons behind this effect are probably multifactorial, but undoubtedly this level of preservation of renal function is noteworthy from a clinical standpoint, especially if this can be replicated in other studies.

Cardiovascular trials with other SGLT2 inhibitors

The ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS; NCT01032629) was designed to evaluate the effects of canagliflozin (100 and 300 mg) on CV events in patients with T2DM and increased CV risk compared with placebo on top of a standard-of-care therapy [51]. The primary endpoint is a three-point MACE, and the study will continue until 420 MACE events have occurred. An interim analysis, done in support of FDA evaluation for market authorization, revealed a numerical increase in CV events in the first 30 days with canagliflozin compared with placebo. Because the number of events was small, the imbalance was attributed to "likely chance events" and did not result in a mention in the canagliflozin label [52]. In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial, the trial's independent data monitoring committee (IDMC) identified an increased risk of leg and foot amputations. The amputations occurred more often in patients treated with canagliflozin compared with patients treated with placebo: 7/1000 patients treated with canagliflozin 100 mg daily, 5/1000 patients treated with canagliflozin 300 mg daily, and 3/1000 patients treated with placebo had amputations. Patients in the CANVAS trial have been followed for an average of 4.5 years to date. Based on an overall assessment, the IDMC has recommended that the CANVAS trial continue. The IDMC has also reported that a second, similar trial evaluating canagliflozin, the CANVAS-R trial, has not shown the same risks of increased leg and foot amputations to date. Patients in the CANVAS-R trial have been followed for an average of 9 months.

All of these observations regarding amputations have resulted in a Safety Alert from the FDA [53].

The Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI; NCT01730534) [54] study is currently the largest CV outcomes trial with an SGLT2 inhibitor. Approximately 17,000 patients with T2DM and either a known CVD (secondary prevention cohort) or two or more CV risk factors (primary prevention cohort) were randomized to dapagliflozin 10 mg or placebo. The primary outcome is a composite of CV death, MI, or ischemic stroke, and the trial is scheduled to complete in 2019 [54]. In the meantime, data from a meta-analysis of CV events from 21 Phase IIb/III dapagliflozin trials are available. This analysis included 9339 patients with T2DM and different levels of CV risk, including CVD, and found no increased CV risk with dapagliflozin use compared with comparators with an HR of 0.79 (95% CI, 0.58–1.07) for the four-point MACE in the overall population and 0.81 (95% CI, 0.56–1.16) in those with a history of CVD [55].

Conclusions

As we are trying to "close the gap of knowledge" in regards to the new SGTL2 inhibitors, the EMPA-REG OUTCOME study results are now discussed in the 2016 position statements from ADA and the AACE/ACE, as well as the Canadian Diabetes Association Clinical Practice Guidelines [2,56,57]. The AACE/ACE algorithm lists SGLT2 inhibitors as neutral with respect to congestive heart failure [2], and the Canadian guidelines have added a column for the effect in a dedicated CV outcomes trial for each medication class and are the first to recommend treatment for a specific subpopulation of patients stating that "In people with clinical cardiovascular disease in whom glycemic targets are not met, an SGLT2 inhibitor with demonstrated cardiovascular outcome benefit should be added to antihyperglycemic therapy to reduce the risk for cardiovascular and all-cause mortality (Grade A, Level 1A for empagliflozin)" [57]. If results from completed studies of other agents in this class confirm the findings of EMPA-REG OUTCOME, it is likely that treatment algorithms will evolve to reposition the SGLT2 class of agents. Because most trials targeting hyperglycemia have failed to show improvements in CV outcomes [58], the results of EMPA-REG OUTCOME are encouraging. Empagliflozin, given on top of a standard-of-care therapy, reduced the composite MACE endpoint, CV mortality, and all-cause mortality in patients with T2DM and established CVD. These findings, coupled with the benefits seen in HF, make empagliflozin an attractive treatment option for patients with T2DM and CVD.

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