

REVIEW

Empagliflozin: Role in Treatment Options for Patients with Type 2 Diabetes Mellitus

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Received: September 12, 2016 / Published online: November 11, 2016
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ABSTRACT

Empagliflozin is an oral treatment for type 2 diabetes mellitus (T2DM), one of the leading causes of death in the US and around the world. Recently, the EMPA-REG OUTCOME study has shown that empagliflozin added to standard of care treatment reduced the risk of cardiovascular (CV) events in patients with T2DM who were also at increased CV risk. The risk of major adverse CV events (MACE: first occurrence of CV death, non-fatal myocardial infarction, or non-fatal stroke) was reduced by

Charles F. Shaefer, Jr, deceased. Dr. Shaefer died after having contributed to early drafts of this manuscript, and the co-authors acknowledge his contribution.

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14% relative to placebo (HR 0.86; 95.02% CI: 0.74–0.99; $P = 0.04$ for superiority). The risk of CV death was reduced by 38% relative to the placebo group (HR 0.62; 95% CI: 0.49–0.77; $P < 0.001$) and the risk of death from any cause by 32% (HR 0.68; 95% CI: 0.57–0.82; $P < 0.001$). Furthermore, empagliflozin was associated with reduced risk of hospitalization for heart failure and of renal adverse events. As well as EMPA-REG OUTCOME, empagliflozin has been studied in a number of clinical trials in patients with T2DM, in various combinations, including with insulin. Empagliflozin has shown significant improvements in glycemic control, body weight, and blood pressure, albeit improvements are limited in patients with declining renal function (estimated glomerular filtration rate < 45 ml/min/1.73 m²). Empagliflozin has been generally well tolerated, with the typical adverse events of genital mycotic infections usually being straightforward to manage. Considering all the data together, empagliflozin appears to be a promising option for many patients with T2DM, but care will still be needed to ensure that use is appropriate for an individual patient's characteristics.

Keywords: Empagliflozin; Hyperglycemia; Hypoglycemia; SGLT2 inhibitor; Type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus is a major cause of mortality around the world [1], ranked as the seventh most common cause of death in the US according to the most recent data available [2]. The actual clinical event that leads to death in people with diabetes is typically cardiovascular (CV) disease, which is thought to account for around half of deaths [1]. Recently, it has been estimated that a 60-year-old male with diabetes but without a history of CV disease (defined for this analysis as myocardial infarction [MI] or stroke) could expect to die 6 years earlier than a similar person without diabetes, while a similar male with diabetes as well as MI or stroke could expect to die about 12 years earlier [3]. About 59% of this reduced life expectancy could be attributed to death from CV causes [3]. In addition to CV disease, diabetes is associated with other serious comorbidities, notably peripheral vascular disease and microvascular complications such as retinopathy, nephropathy, and neuropathy [1].

In type 2 diabetes mellitus (T2DM), which accounts for the vast majority of cases of diabetes, it has been known for some years that treatment to improve glycemic control can reduce the risk of microvascular complications [4, 5]. For CV complications, the benefit of treating hyperglycemia has been less clear—despite epidemiological data showing a direct relationship between increased blood glucose levels and CV disease risk [6]. Intensive glycemic control reduced the risk of MI and of all-cause mortality in newly diagnosed patients in the UK Prospective Diabetes Study (UKPDS),

but only after long-term follow-up (the “legacy” effect) [7]. The UKPDS study began in the 1970s, before the statin era, and whether the same benefit would be seen in patients receiving today’s standard of care is of course unknown. Since the UKPDS study, a number of T2DM drugs have become available, but none have conclusively shown reduced risk of CV events in high-risk patients with T2DM. The drug that probably came closest to demonstrating this was pioglitazone, which showed a 16% relative risk reduction in the secondary endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke [hazard ratio (HR) 0.84, 95% CI: 0.72–0.98; $P = 0.027$] [8]. Unfortunately, this study did not meet its primary endpoint, thought by many to be a dilution of a true effect by inclusion of revascularization in the primary composite. This left the value of the secondary results uncertain and requiring confirmation in a dedicated clinical trial. Thus, based on all the available data, metformin has been recommended as first-line therapy with general principles to customize treatment targets, as well as the drug(s) used, to the needs of individual patients [9, 10].

In 2015, the wait for definitive results ended when the EMPA-REG OUTCOME study reported a lower rate of major adverse cardiovascular events (MACE), CV death, and death from any cause with the relatively new drug empagliflozin versus placebo [11]. Both were added to standard of care in patients with T2DM at high risk for CV events. Given the history of negative or neutral results in CV outcome trials over the preceding years, EMPA-REG OUTCOME generated considerable excitement in the T2DM community. This was the first dedicated trial to show CV benefit of a glucose-lowering therapy in T2DM; subsequently, trials have reported CV benefit with liraglutide [12] and semaglutide [13]. A

further trial has demonstrated reduced risk of stroke or MI with the T2DM drug pioglitazone in patients with a history of cerebrovascular disease and insulin resistance but without T2DM [14].

Following the initial presentation of the EMPA-REG OUTCOME results, specialists around the world have been considering the results and how they might impact treatment decisions in clinical practice. Further analysis showed empagliflozin reduced the risk of hospitalization for heart failure, and this benefit was consistent in patients with and without baseline heart failure [15]. Empagliflozin was also associated with improvements in renal outcomes, including a 39% reduction in new onset or worsening of nephropathy (HR 0.61; $P < 0.001$) [16]. There has been some speculation on whether the benefit seen with empagliflozin may have resulted, at least in part, from factors other than improvements in blood glucose control, such as a hemodynamic or volume effect [17]. This review considers the clinical trial evidence and mechanism of action of empagliflozin, before taking a closer look at the EMPA-REG OUTCOME study and how the results may influence treatment decisions, particularly in primary care practice.

METHODS

To identify publications of clinical trials for empagliflozin for this narrative review, PubMed was searched using the term “empagliflozin” for articles published after 2000 up to 8 August 2016. Results were reviewed to identify all phase 3 trials, including placebo-controlled and active-controlled trials, as well as secondary publications from the EMPA-REG OUTCOME study. No restrictions were placed on other study characteristics, such as number of patients, endpoint, etc. Additional pooled

analyses and relevant review articles were also selected from this list. This article does not contain any new studies with human or animal subjects performed by any of the authors.

GLYCEMIC MECHANISM OF ACTION OF SGLT2 INHIBITORS

Empagliflozin is a member of a class of drugs known as sodium glucose cotransporter 2 (SGLT2) inhibitors. As their name suggests, these drugs inhibit the action of the SGLT2 protein, a glucose transporter found mainly in the proximal tubule of the kidney. SGLT2 is the transporter predominately responsible for reabsorption of glucose from the glomerular filtrate back into the circulation [18].

All available SGLT2 inhibitors are competitive selective inhibitors of SGLT2, although there is some variation among agents in selectivity for SGLT2 over SGLT1, which is the other main glucose transporter in the kidney [19]. By inhibiting SGLT2, these drugs reduce the reabsorption of filtered glucose in the kidney, thus increasing urinary glucose excretion. The kidneys filter around 180 g of glucose every day, and without inhibition, all this glucose is reabsorbed; the majority of glucose is reabsorbed by SGLT2 and a minority by SGLT1 [20]. When SGLT2 inhibitors are used, around a third of this glucose—approximately 60 g/day—will be lost in the urine (it is thought that SGLT1 compensates to some extent for the inhibited SGLT2; hence the majority of glucose is not lost) [21]. The actual amount of glucose excreted will also depend on factors such as the binding affinity of the specific SGLT2 inhibitor and the dose used; for example, with empagliflozin, urinary glucose excretion is about 64 g/day with empagliflozin 10 mg and 78 g/day with empagliflozin 25 mg [22].

In addition to lowering blood glucose levels, SGLT2 inhibitors also have an effect on body weight and blood pressure (BP). The body weight effect is believed to result from lost calories, although patients most likely compensate by increasing their calorie intake, and weight loss stabilizes over time [23]. Reduction in BP probably involves several different pathways, including osmotic diuresis, secondary effects of weight loss, and beneficial changes in arterial stiffness and vascular resistance [24].

With any drug for T2DM, hypoglycemia is a key concern. Mild hypoglycemia can be frightening for patients, but severe hypoglycemia (usually defined as needing the assistance of another person to actively administer carbohydrate, glucagon, or other emergency interventions) can be life threatening [25]. Hypoglycemia may also be linked with other poor outcomes (e.g., the incidence of arrhythmia and possibly death in people with CV disease) [26]. Insulin and drugs that stimulate the secretion of insulin, such as sulfonylureas, are associated with increased risk of hypoglycemia [25]. However, SGLT2 inhibitors do not stimulate insulin secretion and do not tend to increase the risk of hypoglycemia, unless used together with a sulfonylurea or insulin.

EMPAGLIFLOZIN CLINICAL DATA

Blood Glucose Control

Empagliflozin is taken orally and is available in two doses: 10 and 25 mg once daily. It is rapidly absorbed, with limited metabolism, and is excreted primarily unchanged in urine and feces [27]. In patients with T2DM, empagliflozin has been studied as monotherapy and in a number of combination

regimens [28–34]. Most trials have compared empagliflozin with placebo, but a head-to-head study with glimepiride has been reported [29], and one placebo-controlled trial also included a sitagliptin arm as an active comparator [28]. Initial combinations with metformin [35] and fixed-dose combinations with linagliptin have been studied [36, 37]. In addition, empagliflozin has been studied in specific patient groups, namely those with hypertension or renal impairment, as well as the study in patients at high CV risk (EMPA-REG OUTCOME) [11, 38, 39]. Phase 3 studies for empagliflozin are summarized in Table 1.

In these studies, empagliflozin treatment gave clinically significant reductions in glycated hemoglobin (HbA1c) compared with placebo [28, 30–32] and similar reductions to glimepiride [29] and sitagliptin [28]. In the head-to-head study of empagliflozin 25 mg versus glimepiride 1–4 mg (both as add-on to stable metformin), similar changes were seen in the two groups (Fig. 1a) [29]. However, 24% of the glimepiride group had a hypoglycemic adverse event (AE) compared with 2% of the empagliflozin 25 mg group, and the glimepiride group had an increase in body weight (mean 1.6 kg) compared with a weight loss in the empagliflozin group (mean –3.2 kg) [29].

In a 24-week study of treatment-naïve patients with screening HbA1c 7.0–10.0%, empagliflozin also gave similar reductions in HbA1c to the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin (Fig. 1b) [28]. However, in the subgroup of patients with baseline HbA1c \geq 8.5%, empagliflozin at either dose gave larger HbA1c reductions than sitagliptin 100 mg, whereas in patients with baseline HbA1c $<$ 8.5%, reductions remained similar for the empagliflozin and sitagliptin groups (Fig. 1b) [28]. A larger reduction in patients with higher baseline HbA1c values is expected across drug

Table 1 Overview of empagliflozin phase 3 studies

Study	<i>n</i>	HbA1c eligibility	Background therapy	Comparator	Primary efficacy timepoint
EMPA-REG MONO [28]	899	7.0–10.0% ^a	Drug-naïve	Placebo (with sitagliptin 100 mg active comparator)	24 weeks
EMPA-REG MET [30]	638	7.0–10.0% ^a	Metformin	Placebo	24 weeks
EMPA-REG METSU [31]	669	7.0–10.0% ^a	Metformin + sulfonylurea	Placebo	24 weeks
EMPA-REG PIO [32]	499	7.0–10.0%	Pioglitazone ± metformin	Placebo	24 weeks
EMPA-REG H2H-SU [29]	1549	7.0–10.0%	Metformin	Glimepiride (1–4 mg)	2 years
EMPA-REG BASAL [34]	494	>7.0–10.0%	Basal insulin ± metformin ± sulfonylurea	Placebo	18 weeks
EMPA-REG MDI [33]	566	7.5–10.0%	MDI insulin ^b ± metformin	Placebo	18 weeks
Empa-Lina SPC treatment-naïve [36]	677	>7.0–10.5%	Drug-naïve	Component drugs (empagliflozin or linagliptin alone)	24 weeks
Empa-Lina SPC second-line [37]	686	>7.0–10.5%	Metformin	Component drugs (empagliflozin or linagliptin alone)	24 weeks
Empa-Met combination treatment-naïve [35]	1364	>7.0–10.0%	Drug-naïve	Component drugs (empagliflozin or metformin alone)	24 weeks
EMPA-REG BP [38]	825	7.0–10.0%	Various ^c	Placebo	12 weeks
EMPA-REG RENAL [39]	741	7.0–10.0%	Various ^d	Placebo	24 weeks

n = number of patients randomized

GLP-1 glucagon-like peptide-1, *HbA1c* glycated hemoglobin, *MDI* multiple daily injections, *SGLT2* sodium glucose cotransporter 2, *SPC* single-pill combination

^a Otherwise eligible patients with HbA1c >10.0% at screening were assigned open-label empagliflozin 25 mg (in addition to background therapy dependent on the particular study)

^b Total daily dose >60 international units

^c Patients were to be either drug-naïve or pre-treated with any oral antidiabetes therapy, GLP-1 analog, or insulin for ≥12 weeks before randomization

^d Background therapy could not include other SGLT2 inhibitors

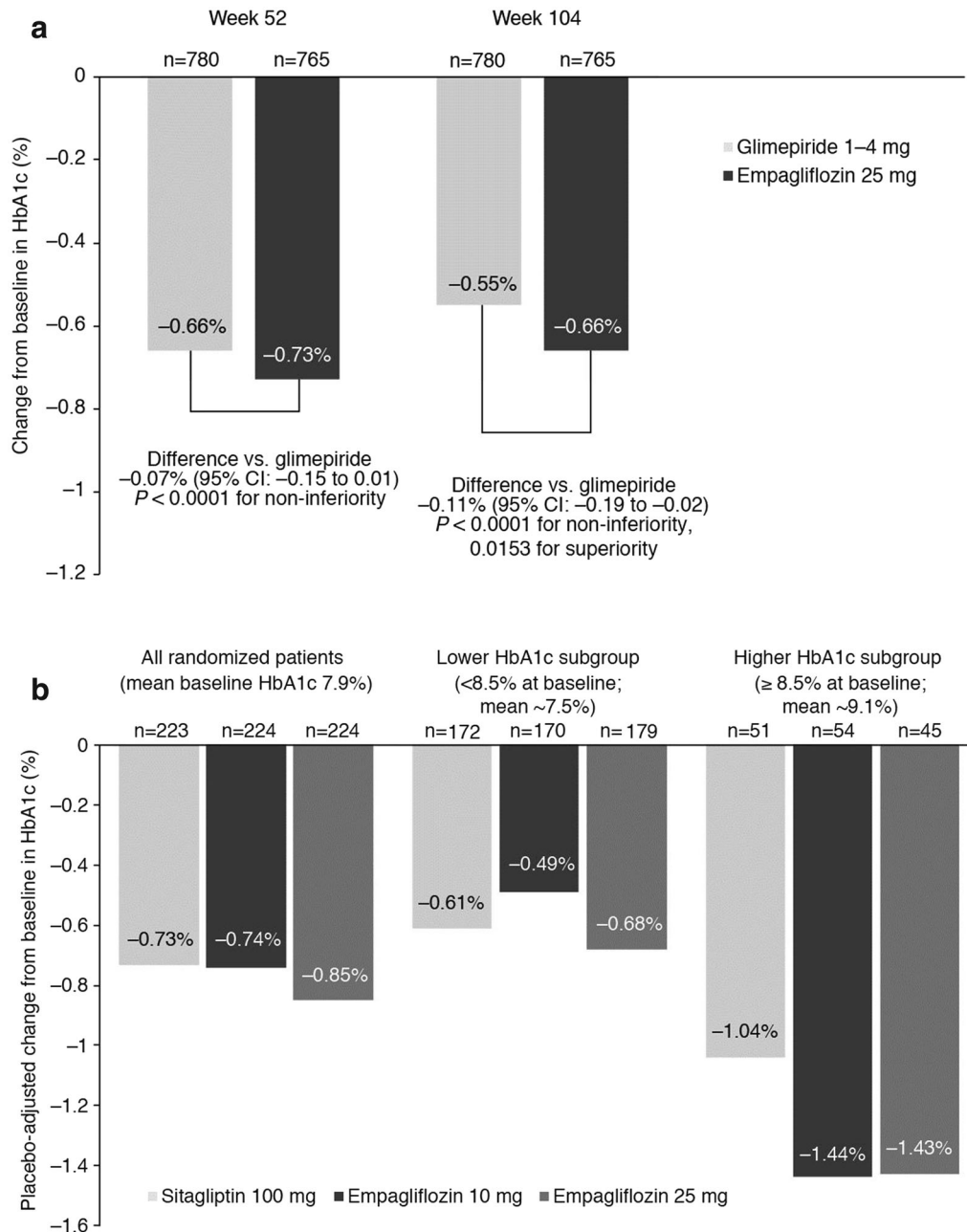


Fig. 1 Changes from baseline in HbA1c. **a** Empagliflozin versus glimepiride: mean maximum dose of glimepiride by week 104 was 2.71 mg (study protocol included titration of glimepiride based on fasting plasma glucose levels, from a starting dose of 1 mg/day to a maximum of 4 mg/day) [29]. **b** Empagliflozin versus sitagliptin: all analyses are at 24 weeks. Note that not all study groups are shown in the figure; in this study, patients were also randomized to placebo, but only comparisons with sitagliptin are shown for clarity. When all patients were analyzed, reductions were similar for empagliflozin and sitagliptin (mean

difference for empagliflozin 10 mg vs. sitagliptin 100 mg: 0.0%, 95% CI: -0.15 to 0.14; $P = 0.9697$; mean difference for empagliflozin 25 mg vs. sitagliptin 100 mg: -0.12, 95% CI: -0.26 to 0.03; $P = 0.1060$). In the subgroup of patients with HbA1c $\geq 8.5\%$, mean reductions with both empagliflozin doses were significantly greater than with sitagliptin (empagliflozin 10 mg vs. sitagliptin 100 mg: $P = 0.008$; empagliflozin 25 mg vs. sitagliptin 100 mg: $P = 0.012$) [28]. *CI* confidence interval, *HbA1c* glycated hemoglobin

classes and has been observed in pooled analysis of empagliflozin data [40]. However, the significantly larger reduction with empagliflozin versus sitagliptin reflects similar results seen with dapagliflozin and saxagliptin, thought to be due to the greater amount of glucose removed by SGLT2 inhibitors at higher plasma glucose concentrations [41].

This increased efficacy at higher baseline HbA1c values is also interesting in terms of the open-label arm of this study. Patients who were otherwise eligible but with screening HbA1c >10.0% were not randomized but instead were all assigned open-label empagliflozin 25 mg [28]. At baseline, mean HbA1c in this group was 11.5%, and by week 24 it had fallen to 7.6%. This mean level is still above the recommended target for most patients, yet 28% of this group reached a goal of HbA1c <7.0% [28]. Although an open-label study such as this must be interpreted with caution, it suggests that empagliflozin may provide useful glycemic improvements across a range of baseline HbA1c values.

Further phase 3 placebo-controlled trials have shown significant reductions in HbA1c when empagliflozin was used as add-on to metformin [30], pioglitazone with or without metformin [32], and sulfonylureas plus metformin [31]. Reductions were of a similar amount to those seen with monotherapy and to those expected for other SGLT2 inhibitors [9]. Empagliflozin has also been studied in twice-daily combinations with metformin (immediate-release) in treatment-naïve patients [35] and fixed-dose combinations with linagliptin in treatment-naïve patients [36] or patients already on stable metformin [37]. Two studies recruited patients on insulin (either basal insulin or multiple daily injections) and both showed significant reductions even in these typically refractory

patients [33, 34]. This demonstrates one of the key features of the mechanism of action—that empagliflozin can be used across the diabetes spectrum since it does not depend on endogenous insulin. Nevertheless, it is worth remembering that many patients with advanced T2DM, and thus likely to be on insulin, will also have some degree of renal impairment, and this can impact the HbA1c reduction. Because of its mechanism of action, empagliflozin relies on adequate renal function to be effective and is contraindicated in people with severe renal impairment, end-stage renal disease, or dialysis. However, empagliflozin has been studied in patients with renal impairment over the range of estimated glomerular filtration rate (eGFR) of 15–90 ml/min/1.73 m² in a 52-week study with the primary endpoint being change in HbA1c after 24 weeks [39]. In patients with eGFR ≥60 to <90 ml/min/1.73 m² [stage 2 chronic kidney disease (CKD)], empagliflozin 10 and 25 mg were both associated with significant reductions in HbA1c versus placebo (−0.52% for empagliflozin 10 mg and −0.68% for empagliflozin 25 mg; both $P < 0.0001$). Patients with eGFR ≥30 to <60 ml/min/1.73 m² (stage 3 CKD) were only randomized to placebo or the higher dose of empagliflozin (25 mg), and again empagliflozin gave a significant reduction in HbA1c compared with placebo, although this appeared more modest than in patients with mild renal impairment (mean −0.42%; $P < 0.0001$). The study included a relatively small number of patients ($n = 74$) with stage 4 CKD (≥15 to <30 ml/min/1.73 m²), and in this group empagliflozin was not associated with significant reductions in HbA1c; in fact, the mean change was a small increase of 0.04%, although the investigators noted reductions in BP and body weight. Overall, this suggests that empagliflozin may

be useful in patients with T2DM and mild or moderate renal impairment, especially since there are relatively few options in this group.

Other CV Risk Factors

In addition to improvements in blood glucose control, clinical trials demonstrated empagliflozin was also associated with significant reductions in body weight compared with placebo, with weight loss of around 2 kg sustained over long-term extension studies (to 76 weeks) [42–45]. Pooled analysis of five clinical trials (3300 patients) also showed reductions in indices of total and visceral adiposity, such as central obesity and the visceral adiposity index, in addition to weight loss and reduced waist circumference [46]. Imaging studies have shown empagliflozin reduced the total fat mass, including abdominal visceral adipose tissue and subcutaneous adipose tissue [29].

Empagliflozin has also been associated with modest reductions in systolic and diastolic blood pressure (SBP/DBP). In a pooled analysis of four 24-week studies (1652 patients on empagliflozin 10 or 25 mg, 825 on placebo), the adjusted mean difference for the pooled empagliflozin groups versus placebo in change from baseline in SBP at week 24 was -3.6 mmHg (95% CI: -4.5 to -2.7 ; $P < 0.001$) and in DBP was -1.3 mmHg (95% CI: -1.9 to -0.8 ; $P < 0.001$) [47]. The results are in line with those of the other available SGLT2 inhibitors [24]. Larger reductions were seen in patients with higher baseline SBP, but empagliflozin was associated with significant reductions in SBP in all three categories of baseline SBP (placebo-corrected mean changes in SBP >140 mmHg group: -6.3 mmHg, SBP 130 – 140 mmHg group: -4.0 mmHg, and SBP

<130 mmHg group: -2.6 mmHg) [47]. Events consistent with volume depletion were reported in 0.2% of patients on placebo and 0.3% of patients on empagliflozin; no such events were reported in patients aged 75 years or older, albeit there were only 66 patients in this subgroup.

Although the majority of patients with T2DM have hypertension, it was not essential for enrollment in empagliflozin clinical trials, nor were concurrent antihypertensive medications held stable during the trial periods. To look at this group specifically, empagliflozin has also been studied in a dedicated trial in patients with hypertension in addition to T2DM [38]. Patients were required to have seated office SBP 130 – 159 mmHg/DBP 80 – 99 mmHg and be on a maximum of two antihypertensive medications that were at stable doses and were continued unchanged throughout the 12-week study. In addition to office BP measurements, patients had ambulatory 24-h BP monitoring before randomization, and again at week 12, with the devices measuring BP and pulse every 20 min. At week 12, both empagliflozin doses gave significant reductions in 24-h SBP (-3.44 mmHg with 10 mg and -4.16 mmHg with 25 mg vs. placebo; both $P < 0.001$) and in 24-h DBP (-1.36 mmHg with 10 mg and -1.72 mmHg with 25 mg; both $P < 0.001$) [38]. In this study, events consistent with volume depletion were reported for one patient (0.4%) in the placebo group, one (0.4%) in the empagliflozin 10 mg group, and none in the empagliflozin 25 mg group, similar to the low proportions seen in the pooled analysis above. The BP reductions in this study and in the pooled analysis were not associated with increases in pulse rate, suggesting empagliflozin may inhibit the sympathetic response [38, 47].

Safety

When selecting a therapy for an individual patient, hypoglycemia risk is usually a key driver [9]. In clinical trials, empagliflozin has not been associated with hypoglycemia, with no increase in risk of confirmed hypoglycemia except when used with background sulfonylurea or fixed-dose insulin [48]. When empagliflozin was given as monotherapy, or as add-on to stable metformin, pioglitazone (with or without metformin), or metformin plus sulfonylurea, no confirmed hypoglycemic AEs that required assistance were reported [48].

For clinical practice, a key question is the proportion of patients likely to discontinue the drug because of AEs. Across a pooled analysis of all empagliflozin randomized clinical trials, including 3695 patients who received placebo, 3806 empagliflozin 10 mg, and 4782 empagliflozin 25 mg, a similar percentage in each treatment group discontinued because of an AE (5.0%, 5.3%, and 5.6% in the empagliflozin 10, 25 mg, and placebo groups, respectively) [48]. The AEs most commonly associated with empagliflozin at either dose have been urinary tract infections and genital mycotic infections [48]. For genital mycotic infections, the association with empagliflozin is clear, with these AEs occurring in 4.7% of the empagliflozin 10 mg group, 5.6% of the 25 mg group, and 1.1% of the placebo group in the pooled analysis [48]. For urinary tract infections, the association is less clear: across the pooled analysis, the incidence was similar across groups [48], but an increased risk has been recorded in some of the individual trials; for example, with monotherapy, events consistent with urinary tract infection were reported in 5% of the placebo group, 7% of the empagliflozin 10 mg group, and 5% of the empagliflozin 25 mg group [28]. In the pooled

analysis, urosepsis was reported in 0.1%, 0.1%, and <0.1% of the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively, and pyelonephritis was reported in 0.1%, <0.1%, and <0.1% of the respective groups, suggesting no increased risk [48]. However, 19 cases of urosepsis and pyelonephritis that started as urinary tract infections in patients taking SGLT2 inhibitors were identified among events reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System database [49]. All cases were hospitalized, and two needed hemodialysis. The database included events reported between March 2013 and October 2014, and as empagliflozin was not available in the US until September 2014, it is not surprising that the reported cases occurred with canagliflozin ($n = 10$) or dapagliflozin ($n = 9$), and the FDA has added warnings and precautions to the labeling for all SGLT2 inhibitors, including empagliflozin. Patients should be advised about signs and symptoms of urinary tract infections, as well as about seeking medical advice, so they can be treated promptly, if appropriate [49].

Other rare events that have been associated with SGLT2 inhibitors following postmarketing reports are ketoacidosis, fractures, and lower-limb amputations (mostly toes). Ketoacidosis was not initially reported in clinical trials with empagliflozin or other SGLT2 inhibitors, and post hoc analysis of pooled empagliflozin trials did not show increased risk [48]. Based on a search for three MedDRA terms, ketoacidosis was identified in 0.1% of the placebo group, 0.1% of the empagliflozin 10 mg group, and <0.1% of the empagliflozin 25 mg group [48]. However, it is possible that in clinical practice, patients have additional predisposing factors compared with patients in clinical trials: 73 cases were reported to the FDA and of these, 15 were reported in

patients with type 1 diabetes mellitus, 1 was in a patient with latent autoimmune diabetes of adults (LADA), and 13 cases did not report the type of diabetes [49]. Although postmarketing cases have been rare, they are serious: all 73 of the cases reported to the FDA were hospitalized or treated in the emergency department [49]. Some—but not all—cases of ketoacidosis in patients on SGLT2 inhibitors have been atypical in that blood glucose levels are not as high as might be expected [50]. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) have recently provided a position statement on this subject, advising that while the risk-benefit profile overwhelmingly favors continued use of SGLT2 inhibitors, awareness of the possible atypical presentation is essential to avoid missed or delayed diagnosis [51].

For fractures, a potential increased risk has been reported for canagliflozin in one long-term trial, although pooled analysis of eight trials showed a similar incidence of fracture with canagliflozin and control arms [52]. The cause is unclear, and various mechanisms have been suggested: effects on phosphorus metabolism, decreases in bone mineral density following weight loss, or possibly an increased risk of falls due to the volume effects of canagliflozin [52]. Although increased fracture risk has not been observed in available pooled analyses for empagliflozin [48] or dapagliflozin [53], the FDA is continuing to evaluate the risk with all available SGLT2 inhibitors [54].

A more recent safety question with canagliflozin has been increased risk of lower limb amputations, mostly affecting the toes. At the time of writing, this has only been seen with canagliflozin, but naturally there will be concern that this may be a class effect [55], and the European Medicines Agency is considering data on all drugs in the class [56]. Details are not yet

available, but the FDA has reported an increase in leg and foot amputations in the interim results of a clinical trial, with most events affecting the toes [55]. While the FDA investigates whether this is a true signal or a chance finding, no change in clinical practice is recommended for canagliflozin. Patients should be monitored for any new pain or tenderness, sores or ulcers, or infections in their feet or legs [55], and this seems reasonable advice to follow with empagliflozin and dapagliflozin also. Indeed, it is reasonable to advise all patients with diabetes to examine their feet and have their practitioner do so as well.

EMPA-REG OUTCOME STUDY

Unlike the trials discussed above, EMPA-REG OUTCOME was designed to study CV events rather than look at measures of glucose control (HbA1c). The trial recruited patients who had T2DM and established CV disease (including peripheral arterial disease), provided they had not had acute coronary syndrome, stroke, or a transient ischemic attack within the 2 months before the study [11]. Patients with established CV disease are of course at increased risk of events, powering the study to demonstrate CV safety while also providing the potential to demonstrate CV benefit.

To be included in the study, patients had to have HbA1c of 7–9% if they were not on glucose-lowering therapy or 7–10% if they were on glucose-lowering therapy. Patients were also required to have eGFR ≥ 30 ml/min/1.73 m². A total of 7020 patients were randomized and treated with empagliflozin 10, 25 mg, or placebo, in addition to any ongoing glucose-lowering therapy. Background glucose-lowering therapy was to remain stable for the first 12 weeks of the study;

thereafter, investigators were encouraged to adjust therapy at their discretion to achieve glucose control according to local guidelines.

Glucose therapy was all on top of standard of care treatment for other risk factors, such as lipid-lowering and antihypertensive medications, to ensure that any effect of the study drug was in addition to available options. At baseline, 95% of patients were on one or more antihypertensive medications and the mean \pm standard deviation SBP/DBP in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups was $135.8 \pm 17.2/76.8 \pm 10.1$, $134.9 \pm 16.8/76.6 \pm 9.8$, and $135.6 \pm 17.0/76.6 \pm 9.7$ mmHg, respectively. Around 80% were on lipid-lowering therapy, and low-density lipoprotein cholesterol at baseline was 84.9 ± 35.3 , 86.3 ± 36.7 , and 85.5 ± 35.2 mg/dl in the respective groups (1 mg/dl = 0.02586 mmol/l). Approximately 90% were on antiplatelet therapy, mainly aspirin. Thus, by most standards these patients were well managed and received incremental benefit on top of the therapy they were already receiving.

The primary outcome measure was time to first occurrence of CV death, non-fatal MI, or non-fatal stroke (3-point MACE), with events independently adjudicated. The study design was event-driven, targeting at least 691 outcome events to provide 90% power to assess whether empagliflozin was non-inferior to placebo (i.e., CV safety) and 80% power to assess superiority (i.e., CV benefit) [57]. For the primary analysis, the two empagliflozin dose groups were to be pooled [57].

Patients were recruited between September 2010 and April 2013; 7020 patients were enrolled and treated at 590 sites in 42 countries [11]. The median treatment time was 2.6 years, and there were 772 primary outcome events overall. As shown in Fig. 2a, patients

receiving empagliflozin had a reduced risk of a primary outcome event, which occurred in 10.5% of the empagliflozin groups versus 12.1% of the placebo group (HR 0.86; 95.02% CI: 0.74–0.99; $P < 0.001$ for non-inferiority, $P = 0.04$ for superiority). The key secondary outcome—a composite of the primary outcome plus hospitalization for unstable angina—also occurred less often in the empagliflozin groups (12.8% of empagliflozin patients and 14.3% of placebo patients, HR 0.89; 95% CI: 0.78–1.01; $P < 0.001$ for non-inferiority, $P = 0.08$ for superiority).

These results were exciting, but even more intriguing were individual components of the primary outcome: the biggest reduction was seen in CV mortality. As shown in Fig. 2b, CV mortality occurred in 3.7% of the pooled empagliflozin group versus 5.9% of the placebo group (HR 0.62; 95% CI: 0.49–0.77; $P < 0.001$). The reduction in risk was seen early in the trial, suggesting a mechanism other than atherosclerosis, since a longer time would be expected before a reduction would be observed. Fatal or non-fatal MI (excluding silent MI) was not significantly reduced, occurring in 4.8% of the pooled empagliflozin group and 5.4% of the placebo group (HR 0.87; 95% CI: 0.70–1.09; $P = 0.23$), again suggesting that the reduction in the primary endpoint was not driven by atherosclerosis. Stroke (fatal or non-fatal) occurred in 3.5% of patients in the empagliflozin combined groups and 3.0% of patients in the placebo group (HR 1.18; 95% CI: 0.89–1.56; $P = 0.26$). When looking at only non-fatal stroke, the confidence intervals again crossed 1 (HR 1.24; 95% CI: 0.92–1.67; $P = 0.16$). What is not yet clear is whether these strokes occurred more frequently in patients with a history of stroke(s) at entry, which would put them at higher risk for subsequent stroke [58]. If so, this could

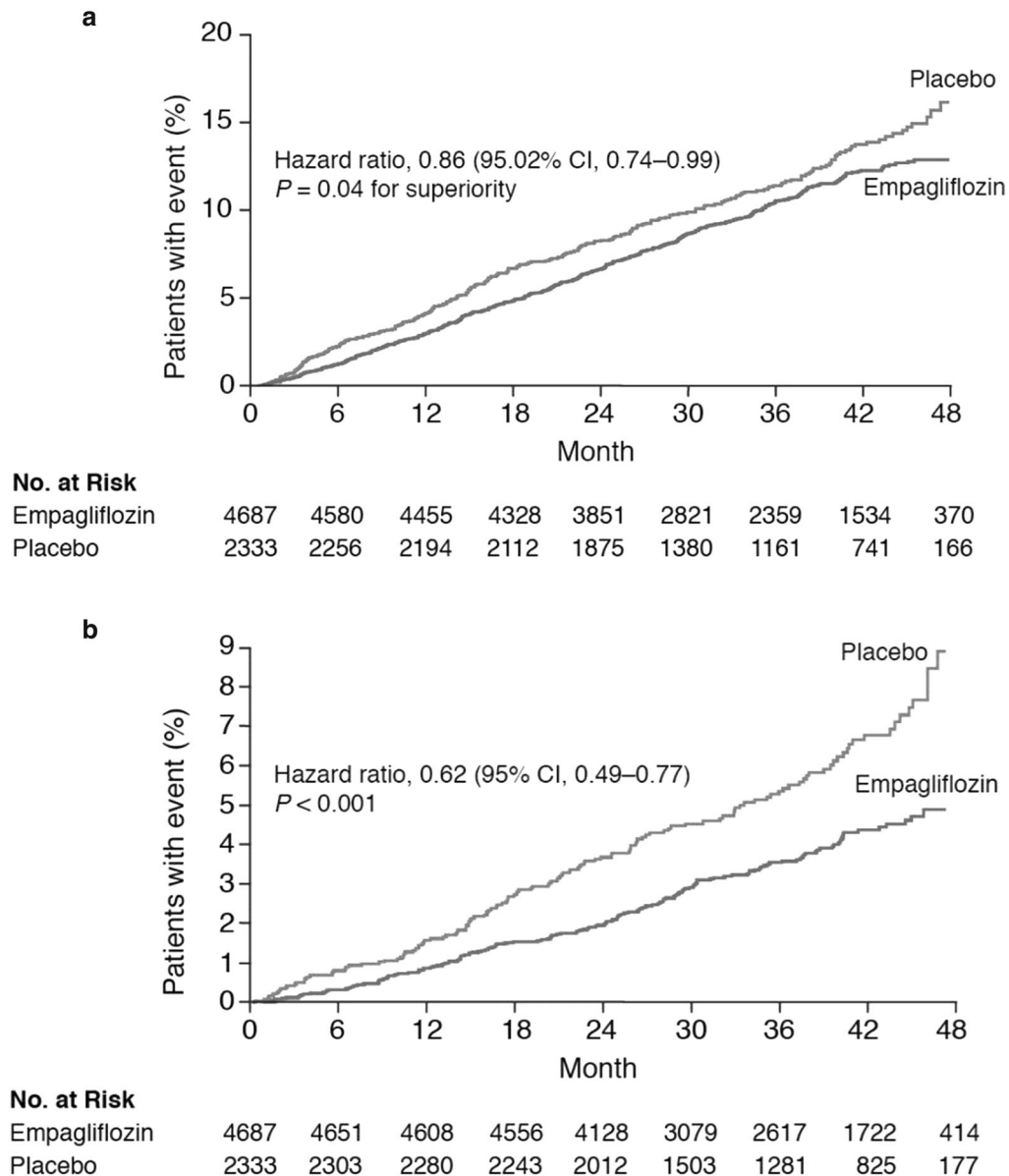


Fig. 2 Cumulative incidence of **a** primary outcome [first occurrence of any of CV death, non-fatal MI, or non-fatal stroke (3-point MACE)] and **b** CV death in the EMPA-REG OUTCOME study. Figures show the pooled empagliflozin groups and placebo group, who received ≥ 1 dose of study drug. Hazard ratios are based on Cox

regression analyses [11]. Copyright 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. *CI* confidence interval, *CV* cardiovascular, *MACE* major adverse cardiovascular events, *MI* myocardial infarction

represent a return to their pre-intervention level of risk for subsequent stroke. The authors did look separately at these patients: of the study population, about 23% ($n = 1084$) had a history of stroke at baseline, and because patients could

have coronary disease as well as stroke, 960 patients had a history of only cerebrovascular disease [11]. Subgroup analysis showed no heterogeneity for the primary outcome or for the risk of death from CV causes, but subgroup

analysis looking specifically at the outcomes of stroke or transient ischemic attack was not published. Any such analyses would of course be post hoc and could only be considered exploratory but would be welcome, especially in light of the effect of empagliflozin on volume events. Recent analysis of glomerular filtration in the EMPA-REG OUTCOME study showed that values increased after the end of the treatment period [16]; although this in itself is considered a good thing, it may reflect underlying changes that could affect the risk of stroke.

In addition to CV mortality, there was also a significant 32% relative risk reduction in all-cause mortality (HR 0.68; 95% CI: 0.57–0.82; $P < 0.001$) [11]. The number of patients who would need to be treated for 3 years with empagliflozin to prevent one death was 39 (Fig. 3) [11]. It is not possible to directly compare the results with those of previous trials, but it is worth considering in context of the numbers needed to treat with statins and antihypertensive drugs [59, 60] and bearing in mind that the reduction with

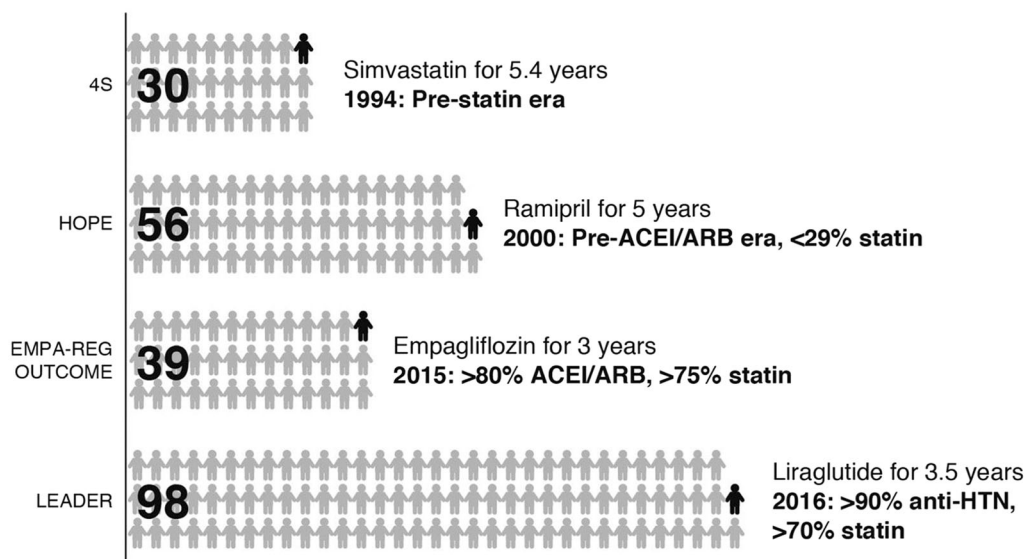


Fig. 3 Number of patients who would need to be treated to prevent one death (from any cause) across different landmark trials in patients with high CV risk. The studies reported were separate trials and not head-to-head comparisons. *4S*: about 5% of patients had diabetes (not specified T1DM or T2DM) [60]. All patients had a history of acute angina or MI (or both). Median follow-up was 5.4 years. The incidence of all-cause mortality during the trial was 11.5% in the placebo group and 8.2% in the simvastatin group. *HOPE*: all patients were aged ≥ 55 years, about 88% had a history of CV disease (8162/9297), and the remainder had diabetes plus at least 1 additional CV risk factor. Of the total group, 38% had diabetes (not specified T1DM or T2DM) [59]. The incidence of all-cause mortality during the trial was 10.4% in the ramipril group and 12.2% in the placebo group. *EMPA-REG OUTCOME*: All patients had T2DM, and

all had a history of CV disease [11]. The incidence of all-cause mortality during the trial was 8.3% in the placebo group and 5.7% in the empagliflozin group (empagliflozin 10 and 25 mg combined). *LEADER*: All patients had T2DM, 81.3% had a history of CV disease, and the remainder had high CV risk (aged >60 years and ≥ 1 other CV risk factor in addition to T2DM) [12]. The incidence of all-cause mortality during the trial was 9.6% in the placebo group and 8.2% in the liraglutide group. The number of patients on all anti-HTN therapy is given because the overall proportion on either ACEIs or ARBs was not reported. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CV* cardiovascular, *HTN* hypertension, *MI* myocardial infarction, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

empagliflozin was seen on top of standard of care treatments. In the LEADER study, the number needed to treat with liraglutide for 3.5 years to prevent one all-cause death was 98 (Fig. 3) [12].

The reduction in the risk of hospitalization for heart failure was also striking, with subgroup analysis showing consistent results in patients with or without heart failure at baseline [15]. Patients with diabetes and heart failure have a particularly poor prognosis [61]; thus, while the results seen with empagliflozin are still to be confirmed by independent studies, they are very promising. Even in patients without diabetes, heart failure is a challenging condition to treat, and it has been reported that empagliflozin will be studied in patients with heart failure, both with and without T2DM [62].

During the trial, renal outcomes were also studied [16]. Patients in the pooled empagliflozin groups had a significantly lower risk of renal disease progression as related to various predefined endpoints, including incident or worsening nephropathy, defined as progression to macroalbuminuria (urinary albumin-to-creatinine ratio >300 mg/g), which occurred in 12.7% of the empagliflozin group versus 18.8% of the placebo group (HR 0.61; 95% CI: 0.53–0.70; $P < 0.001$). The empagliflozin group also had a significantly lower risk of starting renal replacement therapy, which was recorded in 1.0% of the empagliflozin group versus 2.1% of the placebo group (HR 0.45; 95% CI: 0.21–0.97; $P = 0.04$). Empagliflozin appeared to have no effect on the risk of developing albuminuria in patients with normal albumin levels at baseline (HR 0.95; 95% CI: 0.87–1.04; $P = 0.25$), although the risk of progression to macroalbuminuria in the overall group was significantly reduced (HR 0.62; 95% CI: 0.54–0.72; $P < 0.001$). Empagliflozin also

appeared to protect renal function as measured by eGFR—after an initial dip in eGFR during the first few weeks of treatment, eGFR stabilized in the empagliflozin group and in fact returned to baseline values after stopping treatment. Because eGFR in the placebo group declined over time, following the natural progression expected, there were significant differences between the empagliflozin and placebo groups by the study end. It is worth remembering that these renal effects of empagliflozin were seen in addition to standard of care: most patients in the trial were on angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (80.7% at baseline). When looking at adverse events, events that were consistent with acute renal failure, including acute kidney injury, and hyperkalemia were reported in a lower proportion of the empagliflozin group than the placebo group [16].

In the EMPA-REG OUTCOME study overall, the safety profile was much as expected from the clinical trial program, notably increased risk of genital mycotic infections. Confirmed hypoglycemic events, with plasma glucose <70 mg/dl (3.9 mmol/l) or requiring assistance, were reported in similar proportions of the groups, suggesting no increased risk. Events requiring assistance were seen in 1.5% of the placebo group, 1.4% of the empagliflozin 10 mg group, and 1.3% of the empagliflozin 25 mg group. Of the other AEs of interest discussed above, there appeared to be no increased risk of ketoacidosis or of bone fracture; amputations were not reported.

Also as expected from the clinical trial program, empagliflozin was associated with modest reductions in weight and BP, as well as HbA1c. After 12 weeks (the period when background therapies were held stable), mean placebo-corrected HbA1c reductions were

–0.54% in the empagliflozin 10 mg group and –0.60% in the 25 mg group, but more patients in the placebo group received additional glucose-lowering drugs during the trial, and the difference between groups fell (although remaining statistically significant).

Together with the early onset of benefit in CV mortality and the lack of improvement in MI, the small difference in HbA1c levels between the groups suggests an alternative mechanism for the benefit seen with empagliflozin. Suggested mechanisms include the possibility of a diuretic effect causing a decrease in preload and afterload (albeit diuretic drugs have not shown similar results in clinical trials) and an effect on sympathetic tone [63]. Other alternatives include an increase in glucagon, leading to inotropic and antiarrhythmic effects [64], or an increase in ketone production with empagliflozin leading to preferential utilization of ketones by both the heart and kidneys in turn resulting in decreased workload and improved cardiac and renal function [65]. During the trial, small increases were seen in levels of low- and high-density cholesterol, and it is possible that these may have contributed even though the patients were in general well controlled on statins. Indeed, it seems likely that several mechanisms may be working together to cause the overall benefit. Experts continue to debate the possible mechanism, and research to define it may well go on for many years to come. Nevertheless, based on opinion surveys, it appears the results have already had an impact on clinical practice [66].

PLACE OF SGLT2 INHIBITORS IN CLINICAL GUIDELINES

At present, clinical guidelines for diabetes do not distinguish among drugs of the SGLT2 inhibitor

class. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement for the management of hyperglycemia in T2DM recommends a patient-centered approach, selecting treatment strategies (and indeed treatment targets) based on the patient's individual characteristics [9]. This group lists SGLT2 inhibitors along with five other options to use in combination with metformin, although given that there were no available data on CV outcomes with SGLT2 inhibitors at the time this position statement was written, further updates may be expected, perhaps also with the results of the LEADER trial. The ADA 2016 Standards of Care in Diabetes discuss the EMPA-REG OUTCOME study results, noting one of the advantages of SGLT2 inhibitors as a class is the association of empagliflozin with a lower CV disease event rate and mortality in patients with CV disease. However, these guidelines continue to list SGLT2 inhibitors among various options, with the recommendation to select therapies based on individual patient needs [25]. The AACE/ACE consensus statement on management of T2DM is updated annually, and the 2016 update included discussion of EMPA-REG OUTCOME [10]. Again, this group continues to list SGLT2 inhibitors among various agents, although they raised the class in the hierarchy of alternative options.

Why has neither group rushed to recommend empagliflozin as first-line treatment, given the excitement around the results? This is clarified in an interim guideline update by the Canadian Diabetes Association, recently issued in response to the EMPA-REG OUTCOME results [67]. They point out that the patients in EMPA-REG OUTCOME not only had a history of CV disease, but fewer than 2% of patients were drug-naïve, and patients typically

had long-standing diabetes; therefore, for newly diagnosed (drug-naïve) patients, metformin is recommended as the first choice of agent, along with lifestyle therapy. As with other guidelines, individualizing therapy is recommended, but unlike other guidelines, when a second agent is needed, a history of CV disease is prioritized among the patient characteristics, with empagliflozin the current recommended choice of agent in such patients. As with any drug choice, there would be other factors to consider, such as adverse effects, contraindications, and cost, as well as patient preference.

The guidelines added the new recommendation, “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)” [67]. The guidelines refer to selecting an “SGLT2 inhibitor with demonstrated CV outcome benefit” possibly anticipating a class effect when outcome trials for other SGLT2 inhibitors are reported (Table 2).

Table 2 Cardiovascular outcome trials with SGLT2 inhibitors

	EMPA-REG OUTCOME [11]	CANVAS [70]	DECLARE-TIMI 58 [71]	VERTIS CV study [72]
NCT ID	NCT01131676	NCT01032629	NCT01730534	NCT01986881
Study drugs	Empagliflozin 25 mg Empagliflozin 10 mg Placebo	Canagliflozin 300 mg Canagliflozin 100 mg Placebo	Dapagliflozin 10 mg Placebo	Ertugliflozin 15 mg Ertugliflozin 5 mg Placebo
Patients, <i>n</i> ^a	7020	4330	17,276	8000
Key inclusion criteria	History of vascular disease	Aged ≥30 years with history of CV event, or aged ≥50 years with high risk of CV events	Aged ≥40 years with established CV disease and/or multiple risk factors, or males aged ≥55 years/ females aged ≥60 years with ≥1 additional CV risk factor (in addition to T2DM)	History of vascular disease ^b
Primary endpoint	Composite of CV death, non-fatal MI, or non-fatal stroke	Composite of CV death, non-fatal MI, or non-fatal stroke	Composite of CV death, MI, or ischemic stroke	Composite of CV death, non-fatal MI, or non-fatal stroke
Study end ^c	2015	2017	2019	2019

CV cardiovascular, MI myocardial infarction, SGLT2 sodium glucose cotransporter 2, T2DM type 2 diabetes mellitus

^a Actual/estimated (for EMPA-REG OUTCOME, this is the number of patients treated, for the other trials this is an estimate based on information from ClinicalTrials.gov)

^b Defined as evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems

^c Actual/estimated

Among cardiologists, the European Society of Cardiology (ESC) has recently revised their guidelines for CV disease prevention, including an update to the guidance on glucose control in patients with T2DM [68]. Metformin remains the first-line option, but based on the results of the EMPA-REG OUTCOME study, the ESC recommends that an SGLT2 inhibitor should be considered very early in the course of diabetes management in patients with T2DM and existing CV disease [68]. The ESC also updated their guidelines on heart failure to include empagliflozin to prevent or delay the onset of heart failure in patients with T2DM [69]. As with general CV disease prevention recommendations, they continue to recommend metformin as first-line therapy for glycemic control and also point out that intensification of glucose control with agents other than empagliflozin does not reduce the risk of heart failure [69].

Unfortunately, EMPA-REG OUTCOME was not designed to provide information on primary prevention, and such a study is unlikely to be conducted. For the other SGLT2 inhibitors, although the CANVAS and DECLARE trials have included patients both with and without a history of CV disease, in those without a history, high CV risk due to other factors was required [70, 71], and the VERTIS CV study of ertugliflozin includes only patients with a history of atherosclerotic disease [72]. Therefore, at present, the guidelines make sense in the context of considering a history of CV disease as a patient characteristic to guide decisions for individual patients, with empagliflozin, on top of standard of care, considered in such cases. To some extent, treatment decisions will depend on labeling updates for empagliflozin and whether a new indication is likely. The FDA is reviewing the CV

risk reduction data from EMPA-REG OUTCOME and a decision is expected in 2016 [73].

CONCLUSION

So what is the best approach for T2DM patients with a relatively low short-term risk of CV events? Continuing clinical experience is still required, since these are relatively new drugs. None of the CV outcomes trials with SGLT2 inhibitors are likely to inform the use of these agents in such patients. Rather, other considerations, such as impact on weight and SBP as well as glycemic-lowering potential, weighed against typical AEs of genital mycotic infections, will guide the use of empagliflozin for these patients. However, in patients with T2DM and established CVD, based on the EMPA-REG OUTCOME results, empagliflozin is a reasonable option.

ACKNOWLEDGEMENTS

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript; publication support for this article was funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). Writing support was provided by Geraldine Thompson of Envision Scientific Solutions, which was contracted and funded by BIPI. BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations; suggestions were presented to the authors, and minor edits were subsequently implemented. The authors retained final authority on all modifications. All authors had

full access to all of the data in this publication and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures. J.E. Anderson has received advisory panel fees from Abbott Diabetes Care and speaker's bureau and advisory panel fees from Eli Lilly, Boehringer Ingelheim, Sanofi, Janssen, and AstraZeneca.

E. E. Wright, Jr, has received speaker's bureau fees from Eli Lilly, Boehringer Ingelheim, and Abbott Diabetes Care; board member/advisory panel fees from Eli Lilly, Boehringer Ingelheim, Abbott Diabetes Care, Amgen, Voluntas, Polymer Technology Systems (PTS); and consultant fees from Eli Lilly, Boehringer Ingelheim, Abbott Diabetes Care, and Amgen.

C. F. Shaefer Jr had received consultant/speakers bureau fees from AstraZeneca, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Co., Eli Lilly and Co., Janssen Pharmaceuticals, Inc., and sanofi-aventis; and served on the speaker's bureau for VIVUS Inc.

Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

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