

# One Small Step for Empagliflozin, One Giant Leap for Diabetology

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## ABSTRACT

This article discusses the recently published EMPA-REG OUTCOME trial, which assessed cardiovascular outcomes with empagliflozin therapy in persons with type 2 diabetes mellitus and coexisting cardiovascular disease. The article describes the background and challenges of modern cardiovascular outcome trials, points out the strengths of the EMPA-REG OUTCOME study, and places the results in perspective. It highlights the significant impact that these results will have on cardiovascular preventive pharmacotherapy, and on future drug development in diabetes. At the same time, it reminds readers of the limitations of the results, and lists the questions raised by, or left unanswered by, the trial.

**Keywords:** Canagliflozin; Cardiovascular outcomes; Dapagliflozin; Empagliflozin; Sodium-glucose co-transporter 2 (SGLT2) inhibitors; Type 2 diabetes mellitus

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## INTRODUCTION

The EMPA-REG OUTCOME trial (ClinicalTrials.gov identifier, NCT01131676) recently announced the effects of empagliflozin on the cardiovascular outcomes (CVO) and mortality in persons with type 2 diabetes mellitus (T2DM) [1]. In this seminal CVO trial (CVOT), 7020 patients with T2DM with coexisting cardiovascular disease (CVD; myocardial infarction [MI], stroke, or peripheral arterial disease) were randomized to either 10 mg empagliflozin, 25 mg empagliflozin, or placebo, over and above standard of care. The primary composite outcome was a total of three endpoints (death from CV causes, non-fatal MI, and non-fatal stroke), while the key secondary endpoint included a fourth endpoint—hospitalization for unstable angina—in addition to the composite primary endpoint [1].

The results of this study revealed a statistically significant reduction in the primary endpoint with empagliflozin use (10.5% in the empagliflozin group vs. 12.1% in the placebo group; hazard ratio 0.86; relative risk reduction (RRR) 14%, 95% confidence interval 0.74–0.99;  $P = 0.04$ ). Similarly, a RRR

reduction is noted in death from CV causes (RRR 38%; 3.7% vs. 5.9%), hospitalization for heart failure (RRR 35%; 2.7% vs. 4.1%), and all-cause death (RRR 32%; 5.7% vs. 8.3%). However, the difference in rates of non-fatal MI and non-fatal stroke did not reach statistical significance.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

## EARLIER CARDIOVASCULAR OUTCOME TRIALS

Earlier trials have also reported CVO with various glucose-lowering medications. The University Group Diabetes Program (UGDP) study, published nearly half a century ago, highlighted the negative effects of tolbutamide on CV health [2]. The United Kingdom Prospective Diabetes Study (UKPDS), a large study with multiple arms, unearthed the beneficial impact of metformin in contrast to other drugs such as chlorpropamide in improving CVO in T2DM [3]. The STOP-NIDDM trial, breaking new ground, suggested CVO improvement when acarbose was administered to persons with impaired glucose tolerance [4]. Similarly, the PROActive trial on pioglitazone reported a reduction in the composite of all-cause mortality, non-fatal MI, and stroke in patients with T2DM who have a high risk of macrovascular events [5]. However, all of these studies were not designed as a CVOT, and their primary aim was to assess glucose-lowering efficacy rather than improvement in CV health.

Advances in the understanding of the interlink between diabetes and CV disease (CVD), an appreciation of the need to improve

CVO in diabetes care, and the realization that effective glucose-lowering drugs could end up worsening CVO (e.g., muraglitazar [6]), have led to a mandatory requirement for CVOTs in anti-diabetic drugs pending regulatory approval.

It then became imperative for all newly developed glucose-lowering molecules to undergo CV safety analysis by performing a CVOT. The first drug to report such an analysis, after institution of new regulatory requirements, was quick-release bromocriptine, which demonstrated CV safety in a trial which recruited 3070 subjects for a mean follow up of 52 weeks [7]. Since then, various data on dipeptidyl-peptidase 4 inhibitors [8–10] and insulins [11] have been published from large-scale CVOTs which have suggested their CV safety.

While these CVOTs follow similar trial designs and protocols, subtle variations are present [8–11]. Differences in inclusion/exclusion criteria, the duration of follow up, and the choice of primary/secondary endpoints can be easily discerned. Though debate around the validity of various trial designs is never ending, there is broad consensus that modern CVOTs are well designed and have good reliability. All recent CVOTs have been designed to demonstrate CV safety (non-inferiority), rather than superiority, as requested by regulators. This fact should be understood for rational interpretation of their results.

## IMPROVEMENT IN CARDIOVASCULAR CARE

Over the past few decades the standard of care for CV prevention has improved markedly across the globe. Use of medical interventions such as

aspirin, statins, angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and beta blockers has helped to enhance CVO, especially in persons with T2DM. Though widespread use of these standard of care drugs allow easier demonstration of CV safety, their use makes it difficult for a new add-on therapy to demonstrate improvement in CVO.

## EMPAGLIFLOZIN: BETTER BENEFIT

This is exactly what empagliflozin has achieved. In a high-risk cohort of subjects, with over 75% usage of statins, over 80% use of ACEi/ARBs, and over 60% beta-blocker therapy, administration of empagliflozin was able to demonstrate added benefit in terms of CVO [1]. This speaks for the strength of the molecule being studied, as well as the robust quality of trial methodology followed by the authors of the study. Inclusion of a wide variety of high-risk subjects, from 42 different nationalities, enhances the global applicability of these results.

The benefits of empagliflozin were noted early on in the EMPA-REG OUTCOME trial, and continued throughout the study [1]. This finding makes empagliflozin stand apart from other CVD preventive drugs, such as statins and ramipril, which demonstrated a CV benefit after a longer duration of therapy. Whether this means that empagliflozin is an effective drug for secondary prevention of CVD, that is, the prevention of progression of CVD to death is open to debate. Detractors point to the lack of statistical significance noted with respect to occurrence of non-fatal MI and stroke. However, this finding may be thought to reinforce the “preventive power” of empagliflozin: It may even be used in tertiary CVD prevention, as it helps improve outcomes

in persons with T2DM who experience an MI or stroke, ensuring that they survive the acute illness. Thus, empagliflozin may be useful for tertiary prevention, rather than secondary prevention, of CVD. The number needed to treat, (for all-cause mortality), which was 39 for empagliflozin over a period of 3 years, is much lower than that reported for other drugs, including ramipril and simvastatin [12, 13].

The highly significant benefit of empagliflozin ( $P = 0.002$ ) in preventing hospitalization for heart failure raises hope for its use in this clinical situation [1]. This finding is especially welcome considering the controversy related to the increased risk of heart failure hospitalization with other glucose-lowering therapies [14]. Empagliflozin, therefore, gets evidence-backed justification for use not only as a glucose-lowering therapy, but also raises hope for its potential as adjunctive therapy for CVD prevention (Table 1).

## EMPAGLIFLOZIN: EXPANDING BOUNDARIES

The EMPA-REG OUTCOME results should be carefully interpreted to assess their impact on diabetes care and outcomes. While the findings for different subsets of patients need to be studied separately, the EMPA-REG OUTCOME study also throws up a few interesting questions (Table 1). Will these beneficial results be relevant to persons with T2DM and low CV risk, or to persons with type 1 diabetes mellitus? Whether the findings of empagliflozin can be extrapolated to other sodium-glucose co-transporter 2 inhibitors (SGLT2i) are open to discussion. CVOTs are underway for both canagliflozin and dapagliflozin, and their results will decide whether the CV benefits of empagliflozin are a class effect or not [15].

**Table 1** Impact of EMPA-REG OUTCOME study [1]**Strengths**

Robust methodology/clinical design  
 Multinational coverage (42 countries)  
 Applicability across age, gender, CV phenotype  
 Clinically relevant inclusion/exclusion criteria  
 Clear-cut answers from straightforward statistical analysis

**Positive answers**

Empagliflozin is safe in high-risk CV patients with T2DM  
 Empagliflozin improves CV outcomes in high-risk CV patients with T2DM  
 Empagliflozin can be used safely in combination with other vascular-tropic drugs over an extended period of time  
 Empagliflozin can be used for prevention of CVD  
 Empagliflozin does not increase the risk of diabetic ketoacidosis or bone fractures

**Unanswered questions**

Is the beneficial effect of empagliflozin a class effect, or a property unique to this molecule?  
 What are the mechanisms that account for the potential of empagliflozin to reduce CV outcomes?  
 Is the beneficial CV effect of empagliflozin relevant to patients with T2DM and low CV risk, and to patients with type 1 diabetes mellitus?  
 Can empagliflozin be prescribed in acute coronary settings?  
 Can empagliflozin be considered an adjuvant preventive therapy for CVD?

*CV* cardiovascular, *CVD* cardiovascular disease, *T2DM* type 2 diabetes mellitus

It is also uncertain if empagliflozin can be initiated, or continue to be used, in acute coronary settings, including unstable angina, MI, and heart failure. However, while

translating CVOT evidence to practice one should not lose sight of good clinical sense. SGLT2i biology and pharmacology should be understood in detail before prescribing SGLT2i [16]. This therapy should be accompanied by appropriate medication counseling and should not be prescribed to persons at risk of ketoacidosis or recurrent genital infections [17].

**SUMMARY**

While the EMPA-REG OUTCOME study findings should be interpreted carefully to assess their impact on diabetes care and outcomes, the results go far beyond proving the superiority of empagliflozin in improving CVO [1]. The seminal importance of these findings will ensure that this trial acts as a milestone in the fields of diabetology and CV medicine.

The EMPA-REG OUTCOME study raises the bar for future glucose-lowering drugs. It will not now suffice to demonstrate CV neutrality or CV safety. Rather, unequivocal evidence of CV benefits will be required. Such a development will help improve not only CVO, but also diabetes outcomes overall. The EMPA-REG OUTCOME study may be just a small step for empagliflozin, but is a giant leap for diabetes care.

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