

The EMPA-REG OUTCOME study: What does it mean for primary care?

Mark Kennedy, Nicholas Forgione

For the first time, a hypoglycaemic medication has been demonstrated to reduce the rate of cardiovascular (CV) death in people with type 2 diabetes. The EMPA-REG OUTCOME study has shown that empagliflozin is beneficial, not just safe, in terms of CV mortality, even when trialled on a background of near-optimal treatment of blood glucose, lipid and blood pressure levels. However, it also raises many questions, including the mechanisms behind this benefit; whether other patient groups, such as people without established CV disease, would also benefit; and whether this is a class effect attributable to all sodium–glucose cotransporter 2 inhibitors. This article reviews the findings of EMPA-REG and the implications of the study for primary care.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of oral glucose-lowering medication with a novel, insulin-independent mechanism of action. They work by decreasing glucose reabsorption from the proximal renal tubule, thereby increasing urinary glucose excretion. The three agents in this class approved for use in combination therapy in Australia are empagliflozin, dapagliflozin and canagliflozin, but only the first two are currently accessible under the PBS. These medications not only reduce HbA_{1c} levels but also have potentially valuable associated effects, such as weight loss and reduction in blood pressure (BP) without an increase in pulse rate. Other favourable associations have been found, including reductions in markers of arterial stiffness and vascular resistance, albuminuria, visceral adiposity and plasma uric acid levels. The most common side effects are urogenital infections.

Since 2008, the US Food and Drug Administration has required all new antidiabetes drugs to be assessed for cardiovascular (CV) safety. Most CV outcome studies have been designed to test the particular drug compared to a placebo on top of standard care. It is important

to remember that these trials are not primarily designed to assess the effect of glycaemic control on CV outcomes, but to assess CV safety. The results of a number of these studies have been released recently, including TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin; Green et al, 2015), SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombosis in Myocardial Infarction 53; Scirica et al, 2013), EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; White et al, 2013) and ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome; Pfeffer, 2015). None of these trials found either beneficial or adverse effects of these agents on CV mortality compared with placebo. However, SAVOR-TIMI 53 showed an increase in hospitalisation rates for heart failure with saxagliptin, the causation of which is still the subject of debate.

In September 2015, at the European Association for the Study of Diabetes Annual Meeting held in Stockholm, Sweden, the result of the EMPA-REG OUTCOME trial was presented and published simultaneously in the *New England Journal of Medicine* (Zinman et

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Article points

1. The sodium–glucose cotransporter 2 inhibitor empagliflozin has been shown to reduce the risk of cardiovascular (CV) death in people with type 2 diabetes and established CV disease (CVD).
2. Questions remain over the mechanisms behind these benefits, whether empagliflozin would also improve CV outcomes in people without CVD and whether this is a class effect or one unique to empagliflozin.
3. Other trials are likely to answer these questions over time; however, until then, it would appear prudent to selectively prescribe empagliflozin to people with type 2 diabetes and CVD.

Key words

- Empagliflozin
- EMPA-REG OUTCOME
- SGLT2 inhibitors
- Type 2 diabetes

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Page points

1. The EMPA-REG OUTCOME study compared the cardiovascular (CV) safety of empagliflozin 10 mg or 25 mg with that of placebo, all in combination with the standard of care, in people with type 2 diabetes and established CV disease (CVD).
2. The pooled empagliflozin groups showed relative risk reductions in CV and all-cause mortality of 38% and 32%, respectively, compared with placebo.
3. These effects appeared to be independent of effects on HbA_{1c}, body weight and blood pressure (BP), which were optimised in all study arms and in which there were only small differences between the groups.

al, 2015). In this CV trial, empagliflozin, an SGLT2 inhibitor, was compared with placebo in people with established CV disease (CVD) in addition to standard care. This is the first of the CV safety trials involving an SGLT2 inhibitor to be concluded.

The study assessed the effects of two doses of empagliflozin (10 mg and 25 mg) compared with placebo in 7020 people with established CVD being treated with standard care for type 2 diabetes over a median observation period of 3.1 years. The dramatic and unexpected result of this study was a 38% relative risk reduction in CV mortality and a 32% risk reduction in all-cause mortality, largely as a result of the reduction in CV mortality, in the pooled empagliflozin (both doses) groups. What was particularly impressive was that a benefit was seen extremely early – within 3 months. Such early separation of the event curves has not been seen with any other therapy for CVD.

This is the first time a study of an antidiabetes medication has conclusively shown a reduction in CV events in high-risk people. This was also the first of the diabetes CV safety trials designed to test for non-inferiority and then for superiority. Overall, the primary outcome of major adverse cardiac events, defined as a composite of CV death, non-fatal myocardial infarction (MI) and non-fatal stroke, was reduced by 14% compared with placebo. Regarding individual outcomes, no significant difference in the incidence of MI or stroke was observed between empagliflozin and placebo. The incidence of hospitalisation for heart failure was also reduced by 35% in the combined treatment group. Secondary analysis has shown that this finding was strongest in participants without heart failure at trial entry.

Over the course of the study, the empagliflozin recipients showed small reductions in body weight, waist circumference and BP without any increase in heart rate, and a small increase in both HDL- and LDL-cholesterol levels was noted. These effects were insufficient to account for the dramatic reductions in mortality and heart failure, however.

In terms of safety and adverse events, there was no increase in urinary tract infections, hypoglycaemia, renal impairment or volume-

related side effects in the empagliflozin group. However, a higher incidence of genital infections was reported in the pooled empagliflozin groups compared with placebo (6.4% vs. 1.8%). Reassuringly, after recent reports of euglycaemic diabetic ketoacidosis (DKA) in some people with type 2 diabetes treated with SGLT2 inhibitors (Peters et al, 2015), the rate of DKA was only 0.035% in the empagliflozin group, compared to a rate of 0.02% in the placebo group. There was a signal for a slight increase in stroke, most often after the end of the trial, but the difference was not statistically significant. Serious adverse events and discontinuation due to side effects were actually less common in the empagliflozin group, although this difference did not reach statistical significance.

HbA_{1c} was lower in both empagliflozin groups compared to placebo, with adjusted mean differences at week 206 of -2.6 mmol/mol (-0.24%) for the 10 mg dose and -3.9 mmol/mol (-0.36%) for the 25 mg dose compared with placebo. While this modest difference between treatment and placebo might seem disappointing, it is important to understand the design of studies such as EMPA-REG and other recent CV outcome trials for newer diabetes medications. The purpose was not to compare the effects of intensive versus less intensive glucose-lowering treatment on CV outcomes but to assess CV safety. For that reason, empagliflozin or placebo was added to a participant's usual diabetes treatment. In the first 12 weeks of the trial, changes to other diabetes medication was not allowed in order to minimise risk of hypoglycaemia. However, after 12 weeks, investigators were allowed and instructed to add or adjust other diabetes treatment, aiming for appropriate clinical glycaemic targets for each participant. This design was so that the potential for empagliflozin to alter CV event rates could be assessed without the confounding factor of different glucose control between the treatment and placebo groups.

Mechanisms responsible for cardiovascular benefits

There has been intense speculation since the results from EMPA-REG were first announced

as to the mechanism(s) responsible for the significant reduction in CV death. As there was no reduction in the rates of non-fatal MI and non-fatal stroke, the investigators thought it unlikely that the beneficial CV outcomes were due to any effect on atherosclerotic disease.

Effects on glycaemia also seem unlikely to have driven the CV benefit, for a number of reasons. The reduction in HbA_{1c} was very modest (4.9 mmol/mol [0.45%] at week 94 and 3.3 mmol/mol [0.30%] at week 204), as would be expected given that the investigators were free to add other glucose-lowering medications to all treatment arms to achieve appropriate glycaemic targets. We also know from other studies that glycaemic control is a relatively weak contributor to macrovascular benefits in people with type 2 diabetes. In the UKPDS (UK Prospective Diabetes Study Group, 1998), although the microvascular benefits of intensive control became significant early on, it took more than 10 years for the macrovascular benefits to achieve statistical significance. More recent studies, such as ACCORD (Action to Control Cardiovascular Risk in Diabetes; ACCORD Study Group, 2008), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation; ADVANCE Collaborative Group, 2008) and VADT (Veterans Affairs Diabetes Trial; Duckworth et al, 2009), showed no reduction in CV events from intense glycaemic control over follow-up of about 5 years, despite significant microvascular benefits. Remarkably, in EMPA-REG, the separation between the empagliflozin and placebo groups with respect to CV death became obvious 3–6 months into the trial and progressively increased right through to the conclusion of the study. This is inconsistent with the very long periods required to demonstrate such a benefit in previous studies.

The rapid separation of treatment and placebo outcome curves also argues against reductions in BP or weight being the drivers of the outcome benefits. Rather, the rapid reduction in CV events suggests a haemodynamic mechanism of action, mediated through the osmotic diuresis induced by empagliflozin, as a likely cause, whether alone or along with other contributors.

Reductions in both systolic and diastolic BP (5.0/2.5 mmHg) were already significant at 1 month and were maximal at 4 months. At the same time, the reduction in body weight was also nearly maximal at 4 months, reflecting fluid loss and reduced fat tissue. Increases in haematocrit persisted until study end. These changes in BP and intravascular volume occurred quickly enough and persisted to the study end to match the rapid and sustained reduction in CV events. While only 10% of participants had heart failure at study entry, the haemodynamic effects might have treated subclinical heart failure, reducing severity and progression independent of and in addition to other diuretics and treatments for heart failure. This is consistent with the reduction in admissions for cardiac failure seen in the empagliflozin groups.

Other hypotheses abound, and the authors postulated that the mechanisms behind the CV benefits are likely to be multidimensional, including changes in varied factors, including arterial stiffness, cardiac function, cardiac oxygen demand (in the absence of sympathetic nerve activation), cardiorenal effects and reductions in albuminuria and uric acid, along with the established effects on glycaemia, body weight, visceral adiposity and BP.

Generalisability of the findings

It is important to remember that the study population was a very specific one, with established CVD (prior MI, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease) among the inclusion criteria. The mean age of the cohort was over 63 years, and more than half the participants (57%) had a diabetes duration of more than 10 years, both of which are independent risk factors for adverse CV events. Participants were also required to have a BMI ≤ 45 kg/m², an estimated glomerular filtration rate >30 mL/min/1.73 m² (Modification of Diet in Renal Disease equation) and an HbA_{1c} of 53–86 mmol/mol (7–10%) at study entry.

These results support the use of empagliflozin in patients who match those enrolled in the study, specifically those with a history of a previous CV event. What is not yet clear is whether similar results would be seen in different patient groups,

Page points

1. Previous studies of type 2 diabetes therapy suggest that glycaemic control is a relatively weak contributor to macrovascular benefits, especially over the short time frame of EMPA-REG.
2. Reductions in blood pressure and body weight are also unlikely to have directly contributed to the benefits; rather, multiple and additive effects on other parameters are likely to have improved outcomes.
3. Other questions arise as to whether people with type 2 diabetes but without established CVD will also benefit from empagliflozin therapy.
4. For now, these results support the use of empagliflozin in patients who match those enrolled in EMPA-REG.

“While it is quite likely that the beneficial outcomes seen in EMPA-REG will eventually be shown to be a class effect, it would be prudent to selectively choose empagliflozin for people with type 2 diabetes and high cardiovascular risk similar to those enrolled in the study until there is evidence showing similar benefits with other agents.”

such as people without established CVD and those with a shorter duration of diabetes. Over time, subanalysis of the study may also identify specific subgroups of participants who were more or less susceptible to the beneficial effects of empagliflozin owing to unique or previously unrecognised CV abnormalities.

Along with uncertainty about whether the beneficial effects of empagliflozin extend to patient groups beyond those included in EMPA-REG, there is also uncertainty as to whether these effects are unique to empagliflozin or are a class effect expected to be seen with other SGLT2 inhibitors. Other medications in this class have similar long-term CV trials underway, with expected completion dates in the next 2–3 years. CANVAS (Canagliflozin Cardiovascular Assessment Study; Neal et al, 2013) is comparing canagliflozin with placebo, in combination with the standard of care, in more than 4000 people with poorly controlled type 2 diabetes and either a history or a high risk of CV events. It has an expected completion date of June 2017. DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58; Clinicaltrials.gov identifier: NCT01730534) is comparing dapagliflozin with placebo in more than 17 000 people with type 2 diabetes at high risk for CV events receiving standard-of-care treatment. It has an expected completion date of April 2019.

While it is quite likely that the beneficial outcomes seen in EMPA-REG will eventually be shown to be a class effect, it would be prudent to selectively choose empagliflozin for people with type 2 diabetes and high CV risk similar to those enrolled in the study until there is evidence showing similar benefits with other agents.

Conclusion

Approximately half of all deaths in people with type 2 diabetes are caused by heart disease, and the life expectancy of people with type 2 diabetes at high CV risk is reduced by approximately 12 years. Therefore, addressing the burden of CVD is fundamental to the management of diabetes. For the first time, a hypoglycaemic medication has been demonstrated to reduce

the rate of CV death in people with diabetes. The result is even more extraordinary because it occurred on a background of near-optimal treatment of lipid levels and BP.

The EMPA-REG OUTCOME results are very encouraging and clearly have important implications for the treatment of people with type 2 diabetes. However, research is still at an early stage. The study raises a number of questions, including the mechanisms for the reduction in CV mortality, the generalisability of the results to other patient groups and whether these positive results are a class effect. While we await further studies to clarify these questions, we should now be considering empagliflozin for appropriate people with long-standing type 2 diabetes at high CV risk because of its demonstrated benefits.

While it is too early to speculate on the future impact of the EMPA-REG trial, these findings may well result in a significant change in how type 2 diabetes is treated. ■

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