

Time to cardiovascular benefits of empagliflozin: a *post hoc* observation from the EMPA-REG OUTCOME trial

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Abstract

Aims In the EMPA-REG OUTCOME trial, in patients with type 2 diabetes and established atherosclerotic cardiovascular (CV) disease, empagliflozin vs. placebo reduced the risk of hospitalization for heart failure (HHF) by 35%, CV death/HHF by 34%, and CV death by 38%, with an early separation of the cumulative incidence curves. We explored at what time point after randomization these benefits became apparent.

Methods and results We expressed time trajectories for the effect of pooled empagliflozin doses vs. placebo on HHF, CV death/HHF, and CV death based on hazard ratios (95% confidence interval) and calculated the hazard ratio on the day the effect reached significance using Cox proportional hazards models. Overall, 7020 patients aged ≥ 18 years were treated with empagliflozin 10 mg ($N = 2345$), empagliflozin 25 mg ($N = 2342$), or placebo ($N = 2333$) once daily in addition to standard of care. Mean age (years \pm SD) was 63.1 ± 8.6 , and 72% were male. The benefit of empagliflozin on CV death first reached statistical significance on Day 59 (HR [95% confidence interval]) (0.28 [0.08, 0.96], $P = 0.0424$) and was generally sustained throughout the trial (overall 0.62 [0.49, 0.77], $P < 0.0001$). Risk reduction with empagliflozin on HHF reached statistical significance on Day 17 (0.10 [0.01, 0.87], $P = 0.0372$) and was sustained throughout the study (overall 0.65 [0.50, 0.85], $P = 0.0017$). For the composite outcome of CV death or HHF, risk reduction with empagliflozin reached statistical significance on Day 27 (0.28 [0.08, 0.97], $P = 0.0445$) and was sustained throughout follow-up (overall 0.66 [0.55, 0.79], $P < 0.0001$).

Conclusions In EMPA-REG OUTCOME, the benefit of empagliflozin in reducing the risk of HHF, CV death/HHF, and CV death emerged within weeks after treatment initiation. The earliest benefit appears to be on HHF.

Keywords Cardiovascular outcomes; Empagliflozin; Heart failure; Type 2 diabetes

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Background

Timely reduction of cardiovascular (CV) events in type 2 diabetes (T2D) remains a priority of pharmacological therapies. This is particularly important in those with established CV disease, in whom the risk of recurrent events, some of which

occur early, is increased. Prior studies have clearly demonstrated that patients with T2D and a history of a prior ischaemic event are at substantial risk of subsequent events and CV death.^{1,2} Recent analyses suggest that intensive blood pressure control improves outcomes in T2D, with the Kaplan–Meier curves separating at approximately 1 year.³ Similarly,

intensive low-density lipoprotein cholesterol lowering and other therapies that target atherosclerosis improve outcomes in T2D with the separation of the event curves appearing to also occur at about 1 year after randomization.⁴ Meanwhile, sodium-glucose co-transporter-2 (SGLT2) inhibitors have demonstrated robust benefits on CV outcomes with a much earlier treatment effect.

In the EMPA-REG OUTCOME trial,⁵ empagliflozin reduced the risk of hospitalization for heart failure (HHF) by 35%, CV death by 38%, and the composite of CV death or HHF by 34% in patients with T2D and established atherosclerotic CV disease (ASCVD). The reduction in risk of HHF seemed to occur early.⁶

Aims

In the current *post hoc* analyses, we aimed to explore at what time point after randomization these benefits became statistically significant.

Methods

In EMPA-REG OUTCOME, individuals aged ≥ 18 years with T2D, established ASCVD, and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m² were randomized. A clinical event committee prospectively adjudicated all CV and mortality events (including HHF). We expressed time trajectories for the effect (hazard ratios, HRs [95% confidence interval]) of pooled empagliflozin doses vs. placebo on CV death, first HHF, and the composite of CV death or HHF (excluding fatal stroke). We calculated the HR on each day following randomization until the last observation of the last patient using the Cox proportional hazards model that included terms for treatment, age, sex, baseline body mass index, baseline estimated glomerular filtration rate, baseline glycated haemoglobin, and geographical region. Thereby, all events until the respective day were considered and patients without events were censored at the respective day. We then assessed the timing when the treatment effect first reached statistical significance based on a *P*-value of < 0.05 .

Results

A total of 7020 patients received double-blind treatment with empagliflozin 10 mg (*N* = 2345), empagliflozin 25 mg (*N* = 2342), or placebo (*N* = 2333) once daily in addition to standard of care. Mean age (years \pm SD) was 63.1 ± 8.6 , and 72% were male. The benefit of empagliflozin on CV death was first statistically significant at Day 59 (HR [95% confidence interval]) (0.28 [0.08, 0.96], *P* = 0.0424) and was largely sustained during

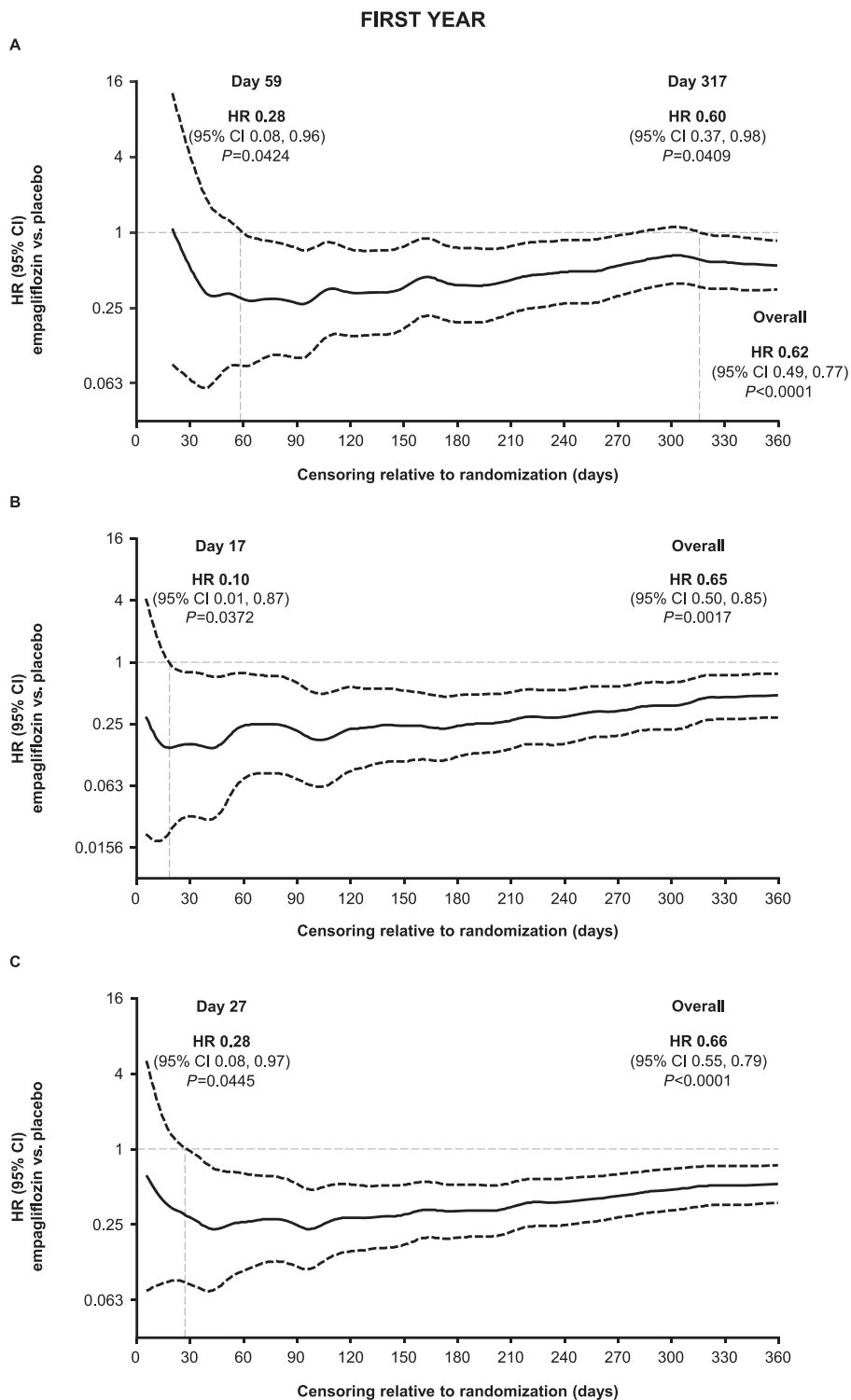
follow-up. A transient loss of significance was seen at around Day 300, followed by sustained effect throughout the duration of the trial, with an overall HR of 0.62 (0.49, 0.77), *P* < 0.0001. For the outcome of HHF, the risk reduction with empagliflozin vs. placebo reached statistical significance at Day 17 (0.10 [0.01, 0.87], *P* = 0.0372) with sustained significance throughout the study and an overall HR of 0.65 (0.50, 0.85), *P* = 0.0017. Similarly, for the composite outcome of CV death or HHF, the risk reduction with empagliflozin reached significance at Day 27 (0.28 [0.08, 0.97], *P* = 0.0445) and was sustained throughout follow-up with an overall HR of 0.66 (0.55, 0.79), *P* < 0.0001 (Figure 1).

Conclusions

While several mechanisms have been suggested to explain the benefits of SGLT2 inhibitor therapy on CV events, mediation analyses from EMPA-REG OUTCOME suggested that the strongest mediator of the reduction in CV death was the rise in haematocrit (and haemoglobin), potentially reflecting haemoconcentration.⁷ While a reduction in plasma volume (leading to improved left ventricular [LV] filling pressures and decreased wall stress) may partially explain this phenomenon, recent data suggest that increased erythropoiesis may also contribute to the rise in haematocrit, because within a month of empagliflozin treatment, erythropoietin levels are significantly increased.⁸ Conceivably, this endogenous increase may improve myocardial oxygen delivery to the ischaemic heart and also improve ventricular performance (although exogenous therapy with erythropoiesis-stimulating agents in patients with chronic kidney disease has actually been linked to *increased* mortality).⁹

In addition, empagliflozin vs. placebo has been shown to produce a significant reduction in LV mass index in people with T2D and coronary artery disease. These beneficial effects on LV mass regression were observed early, over a 6-month treatment period.¹⁰ The emergence of such early benefits of empagliflozin treatment has important implications. Added to appropriate background therapy (with statins, inhibitors of the renin-angiotensin system, blood pressure control, and anti-platelet therapy), patients with T2D and ASCVD can derive morbidity and mortality benefits of empagliflozin shortly after treatment initiation. Prevention of HF is particularly important because the prevalence of HF in populations with T2D seems to be rising and because control of traditional CV risk factors such as glucose, blood pressure, and lipids seems to be more effective in preventing atherosclerotic events than HF events.^{3,4,11–13} In patients with HF and reduced ejection fraction, a similar early benefit on CV death or worsening HF was observed in those treated with dapagliflozin¹⁴ and in those treated with empagliflozin vs. placebo.¹⁵ Also in such populations, cardiac remodelling

Figure 1 Smoothed curves for successive hazard ratios (HRs; 95% confidence intervals [CI]) for empagliflozin vs. placebo for (A) cardiovascular death, (B) hospitalization for heart failure, and (C) hospitalization for heart failure/cardiovascular death (excluding fatal stroke) with a vertical line demonstrating the day the benefits reach statistical significance. HRs and 95% CIs are shown in relation to time point of censoring — treated set. Overall results apply to the complete study duration.



appears to be impacted by empagliflozin: in two smaller mechanistic trials, reductions in LV diastolic and end-systolic volumes were observed following 6 months and 36 weeks of treatment with empagliflozin vs. placebo.^{16,17} Added to this, a recent study reported that empagliflozin was safe and well tolerated also when initiated in the acute setting of worsening HF in patients with HF and reduced ejection fraction, further supporting the early benefit–risk profile of SGLT2-inhibitors.¹⁸

In summary, this *post hoc* analysis demonstrates that empagliflozin exerts clinically and statistically significant CV benefits within weeks of treatment initiation, which are sustained long term. This information may aid clinicians, by providing a framework for therapeutic decisions to prioritize and individualize therapies in an effort to reduce CV and mortality risk expeditiously. It may also help patients with T2D and established ASCVD to recognize the potential for rapid benefit from prescribed therapy.

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Conflict of interest

S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery. S.V. has also received grants and personal fees for speaker honoraria and advisory board participation from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Amgen, HLS, Merck, EOCI Pharmacomm Ltd, Novartis, Sun Pharmaceuticals, and Toronto Knowledge Translation Working Group. He also serves as President of the Canadian Medical and Surgical Knowledge Translation Research Group. L.A.L. has received research funding from, has provided CME on behalf of, and/or has acted as an advisor to AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Lexicon, Merck, Novo Nordisk, Sanofi, and Servier B.Z. and has received research grants awarded to his institution from Boehringer Ingelheim and honoraria from Janssen, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Novo Nordisk, and Merck. A.S. has received funding from the FRSQ-Junior 1 Scholars program,

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Author contributions

S.V. wrote the first draft. All authors fulfil the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, are fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version of the manuscript. M.M. provided statistical expertise. M.M. and S.V. are the guarantors of this work.

Data availability statement

The sponsor of the EMPA-REG OUTCOME trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the following website: <https://trials.boehringer-ingelheim.com>.

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