Cardiovascular and major journals

EMPA-REG: Empagliflozin's benefits were not driven by participants with pre-existing heart failure

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Heart failure is a highly prevalent comorbidity with diabetes, occurring in more than one in five people with the condition aged over 65 years (Bertoni et al, 2004). Furthermore, it is associated with a very poor prognosis, with a median survival time of around 4 years. Recently, there has been considerable debate around the effects of different blood glucose-lowering therapies on heart failure outcomes in type 2 diabetes, while intensive glucose control has failed to demonstrate any benefit with respect to heart failure outcomes.

Empagliflozin is a sodium–glucose cotransporter 2 (SGLT2) inhibitor and as such reduces renal glucose reabsorption, thus increasing urinary glucose excretion. The recently published EMPA-REG OUTCOME study demonstrated that treatment with empagliflozin added to standard care reduced the risk of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke; cardiovascular mortality; hospitalisation for heart failure; and overall mortality compared with placebo in 7020 people with type 2 diabetes and high cardiovascular risk (Zinman et al, 2015).

This particular subanalysis of EMPA-REG (summarised alongside) focussed on heart failure and hospitalisation outcomes in the overall study population and in subgroups defined according to baseline characteristics. Participants were randomised to receive empagliflozin 10 mg, empagliflozin 25 mg or placebo. Of the 7020 participants, 706 (10.1%) had heart failure at baseline. The composite outcome of heart failure hospitalisation or cardiovascular death occurred in a significantly lower proportion of empagliflozin recipients compared with placebo (5.7% vs 8.5%; hazard ratio [HR], 0.66). This corresponded to a number needed to treat of 35 to prevent one heart failure hospitalisation or cardiovascular death over 3 years. Consistent effects of empagliflozin were observed across subgroups defined by baseline characteristics, including people with or without heart failure, and across categories of medications to treat diabetes and/or heart failure.

Empagliflozin improved other heart failure outcomes, including hospitalisation for or death from heart failure (2.8% vs 4.5%; HR, 0.61) and was associated with a reduction in all-cause hospitalisation (36.8% vs 39.6%; HR, 0.89). In both treatment groups, serious adverse events and adverse events leading to discontinuation were more common in people with heart failure at baseline than in those without it, but they were no more common with empagliflozin than with placebo. Empagliflozin appeared to reduce the risk of the primary outcome to the same extent in people with heart failure at baseline – who had high use of medications used to treat heart failure – as in those without pre-existing heart failure. Thus, the positive outcomes associated with empagliflozin do not appear to have been predominantly driven by this patient group.

The effects of empagliflozin on heart failure hospitalisation or cardiovascular death and on all-cause hospitalisation was observed very early in the study and was sustained throughout the trial. This suggests that the benefit was not driven by an effect on atherosclerosis; however, the mechanisms behind these observations remain unknown. Potential contributors include osmotic diuresis; effects on plasma volume and sodium retention; reductions in arterial stiffness and rate pressure product; reductions in weight and blood pressure without increases in sympathetic nervous activity; reductions in hyperglycaemia and insulin levels; and reductions in uric acid.

There are some limitations to these data, primarily concerning the validity of the diagnosis of heart failure at baseline and the absence of objective measures of ventricular function. Nevertheless, the data provide further evidence in support of the potential cardiovascular benefits of SGLT2 inhibitor therapy, although the generalisability to wider patient populations remains the focus of ongoing studies of these agents. ■

References on opposite page

Eur Heart J

EMPA-REG subanalysis: Heart failure outcomes

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this article, the authors report further analyses of the EMPA-REG OUTCOME study of empagliflozin in people with T2D. The analyses include heart failure (HF) and hospitalisation outcomes as well as subanalyses according to baseline characteristics.

2 Over a median treatment duration of 2.6 years and an observation time of 3.1 years, the composite outcome of cardiovascular (CV) death or hospitalisation for HF was significantly less common with empagliflozin than with placebo (5.7% vs 8.5%; hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.55–0.79).

3 The composite endpoint of hospitalisation for or death from HF was also significantly less common in the empagliflozin group (2.8% vs 8.5%; HR, 0.61; 95% CI, 0.47–0.79).

4 At baseline, 244 placebo recipients (10.5%) and 462 empagliflozin recipients (9.9%) had HF.

5 The incidence of HF hospitalisation, CV death and all-cause mortality was two- to six-fold higher in participants with HF at baseline compared to those without it. However, the reductions in risk of these outcomes associated with empagliflozin were consistent in the two subgroups.

6 The risk of adverse and serious adverse events was greater in people with HF at baseline; however, in this subgroup, the risk was lower in empagliflozin than placebo recipients.

7 In conclusion, these findings suggest that the outcomes observed in EMPA-REG were not driven by participants with pre-existing HF.

Fitchett D, Zinman B, Wanner C et al (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* **37**: 1526–34

BMJ

RAAS blockers not superior to other antihypertensives for diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this systematic review and meta-analysis of 19 studies (n=25 414), renin–angiotensin–aldosterone system (RAAS) blockers were compared with other antihypertensives in terms of cardiovascular outcomes in people with diabetes.

2 No significant differences were found in terms of all-cause or cardiovascular mortality, myocardial infarction, angina, stroke, heart failure (HF) or end-stage renal disease.

3 The one exception was that RAAS blockers were superior to calcium channel blockers in preventing HF; however, these results were mainly driven by one study that has previously been criticised.

4 These findings support the current European Society of Cardiology recommendation that any class of hypertensive agent can be used in people with diabetes who do not have renal impairment.

Bangalore S, Fakheri R, Toklu B, Messerli FH (2016) Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* **352**: i438

Diab Vasc Dis Res

Reduced CVD risk with combined reductions in HbA_{1c}, BP and lipids

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 These authors assessed the risk of cardiovascular disease (CVD) in 13 477 people with T2D according to whether they had reductions or increases in HbA_{1c}, blood pressure (BP) and non-HDL cholesterol levels over a mean follow-up of 6.5 years.

2 The reference group comprised people who had increases in all three parameters (n=6757). Compared with this group, people who had a reduction in HbA_{1c} but increases in the other two parameters (n=1925) had a CVD hazard ratio (HR) of 0.65.

3 People who achieved reductions in HbA_{1c} and BP, but who had increases in lipids (n=2050), had an HR of 0.44, and those who achieved reductions in all three parameters (n=2745) had an HR of 0.25.

4 Similar patterns were observed for coronary heart disease and all-cause mortality.

Eeg-Olofsson K, Zethelius B, Gudbjörnsdottir S et al (2016) Considerably decreased risk of cardiovascular disease with combined reductions in HbA_{1c}, blood pressure and blood lipids in type 2 diabetes: Report from the Swedish National Diabetes Register. *Diab Vasc Dis Res* **13**: 268–77

BMJ

Antihypertensives may increase mortality in people with SBP <140 mmHg

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 In this systematic review and meta-analysis of 49 trials (73 738 participants), antihypertensive treatment in people with diabetes and a baseline systolic blood pressure (SBP) of ≥140 mmHg was found to reduce the risk of all-cause and cardiovascular (CV) mortality, myocardial infarction and stroke.

2 However, if baseline SBP was <140 mmHg, treatment had no benefit and actually increased the risk of CV death (relative risk [RR], 1.15; 95% confidence interval [CI], 1.00–1.32).

3 Similar patterns were observed for attained, not just baseline, SBP.

4 The authors conclude that, while BP treatment is strongly supported in people with diabetes and an SBP ≥140 mmHg, treatment may be harmful in those with an SBP <140 mmHg, and that BP goals should be less aggressive in people with diabetes than in the general population.

Brunström M, Carlberg B (2016) Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* **352**: i717

N Engl J Med

ELIXA: CV safety of lixisenatide confirmed

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 These are the results of the ELIXA (Evaluation of Lixisenatide in Type 2 Diabetes and Acute Coronary Syndrome) trial to assess the cardiovascular (CV) safety of the glucagon-like peptide-1 receptor agonist lixisenatide.

2 A total of 6068 people with T2D who had had a myocardial infarction (MI) or unstable angina were randomised to receive lixisenatide or placebo in addition to standard care.

3 Over a median follow-up of 25 months, the incidence of the primary endpoint – a composite of death from CV causes, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina – was similar in the two groups 13.4% vs 13.2%; hazard ratio, 1.02; 95% confidence interval, 0.89–1.17).

4 In terms of these outcomes, lixisenatide was found to be non-inferior, but not superior, to placebo.

5 Small but significant improvements in HbA_{1c} and body weight were also observed in the lixisenatide group, despite optimal background treatment occurring in both groups.

Pfeffer MA, Claggett B, Diaz R et al (2015) Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* **373**: 2247–57

"These findings support the current European Society of Cardiology recommendation that any class of hypertensive agent can be used in people with diabetes who do not have renal impairment."

References from commentary

Bertoni AG, Hundley WG, Massing MW et al (2004) Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* **27**: 699–703

Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* **373**: 2117–28