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Totality of evidence in trials of sodium–glucose co-transporter-2 inhibitors in the patients with heart failure with reduced ejection fraction: implications for clinical practice

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Sodium–glucose co-transporter-2 (SGLT2) inhibitors exert favourable effects on the heart and kidney that cannot be explained by their glucose-lowering effect. In five trials with four different agents, SGLT2 inhibitors reduce the risk of heart failure hospitalizations and mitigate the progression of chronic kidney disease in patients with type 2 diabetes.^{1–3} Other antihyperglycaemic agents do not exert these benefits within 1–2 years of the onset of treatment, even though many have greater effects to lower blood glucose.⁴

Benefits on heart failure events in trials of sodium–glucose co-transporter-2 inhibitors in type 2 diabetes, with or without heart failure

When the findings in trials in diabetes are combined, treatment with SGLT2 inhibitors is accompanied by $\approx 30\%$ reduction in the risk of heart failure hospitalization and a $\approx 40\text{--}50\%$ reduction in the risk of serious adverse renal events, including the development of end-stage kidney disease.¹ The magnitude of these benefits is consistent across the various trials, and the effects are statistically robust and clinically important. However, in contrast to these striking effects on non-fatal events, these drugs have inconsistent effects on mortality. Depending

on the trial, estimates of a treatment effect on survival have varied from virtually no reduction to as high as $\approx 40\%$ decrease in risk.^{5,6} Accordingly, when the effects of SGLT2 inhibitors on cardiovascular death in individual trials were combined in a meta-analysis, the magnitude of the mortality benefit was modest (a 15% reduction in risk) and characterized by significant heterogeneity.¹

The consistency of the effect on non-fatal heart failure events and the inconsistency of the effect on cardiovascular death is well-illustrated in two trials with dapagliflozin and empagliflozin in type 2 diabetes (DECLARE-TIMI58 and EMPA-REG OUTCOMES, respectively), Table 1. Both trials demonstrated a similar and robust reduction in the risk of heart failure hospitalizations as well as a decrease in the risk of clinically important progression of renal disease.^{5,6} However, when all randomized patients are considered, SGLT2 inhibition reduced the risk of cardiovascular death by 38% in the trial with empagliflozin but by only 2% in the trial with dapagliflozin. When the analysis is confined to comparable groups of patients (i.e. those with a prior myocardial infarction), the risk reductions for cardiovascular death were 41% in the trial with empagliflozin and 8% in the trial with dapagliflozin.^{7,8} These two estimates represent opposite extremes of the pooled estimate of a 15% reduction in the risk of death reported in a meta-analysis.¹

Most of the patients in the trials of SGLT2 inhibitors in type 2 diabetes did not have heart failure at the time of enrolment, and the phenotype of heart failure was not well-characterized. Since the

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investigators did not routinely perform cardiac imaging, it was unclear if the effect of these drugs to reduce heart failure events applied to patients with a reduced or preserved ejection fraction. However, in the DECLARE-TIMI58 trial, the benefit on cardiovascular death or hospitalization for heart failure was greater in those with reduced ejection fraction than with a preserved ejection fraction at baseline (hazard ratio 0.62, 95%CI 0.45–0.86 and 0.88, 95%CI 0.76–1.02, respectively, interaction $P = 0.046$).⁹ The benefit was particularly striking in those with an ejection fraction $\leq 30\%$.

In addition to a lack of information regarding the phenotype of heart failure, the trials of SGLT2 inhibitors in type 2 diabetes provided little insight about the concomitant use of drugs that are known to prolong survival in patients with heart failure. Therefore, it was not known whether SGLT2 inhibitors would reduce risk of heart failure hospitalizations if patients had received optimal treatment for heart failure. Although many patients in the trials of type 2 diabetes were receiving inhibitors of the renin-angiotensin system and beta-adrenergic receptor blockers, most were not receiving mineralocorticoid receptor antagonists or neprilysin inhibitors. In one trial, concomitant treatment with spironolactone and eplerenone appeared to attenuate the ability of SGLT2 inhibitors to reduce heart failure events.¹⁰ Furthermore, because the cardiovascular outcome trials in type 2 diabetes were carried out before the availability of sacubitril/valsartan, it was not clear how inhibitors of SGLT2 and neprilysin might interact. Therefore, it was important to carry out large-scale definitive trials of SGLT2 inhibitors in patients with well-characterized heart failure who were taking all appropriate treatments for heart failure, including the use of cardiac devices.¹¹

Benefits on heart failure events in trials of sodium–glucose co-transporter-2 inhibitors in patients with heart failure and a reduced ejection fraction, with or without type 2 diabetes

Two large-scale trials of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction have now been completed, Table 1. The DAPA-HF and EMPEROR-Reduced trials both enrolled patients with classes II, III, and IV heart failure due to an ischaemic or non-ischaemic cardiomyopathy who were routinely treated with inhibitors of the renin-angiotensin system and beta-blockers, and (in the majority of patients) with mineralocorticoid receptor antagonists.^{12,13} Half of the patients in each trial did not have type 2 diabetes. Compared with the DAPA-HF trial with dapagliflozin, the EMPEROR-Reduced trial with empagliflozin was enriched for patients with more severe disease, i.e. patients in EMPEROR-Reduced had lower ejection fractions (27% vs. 31%), higher levels of N-terminal prohormone B-type natriuretic peptide (NT-proBNP) (≈ 1900 vs. ≈ 1450 pg/mL) and lower glomerular filtration rates (62 vs. 66 mL/min/m²), and were more likely to be treated with sacubitril/valsartan ($\approx 20\%$ vs. $\approx 10\%$). Accordingly, the rate per 100 patient-years of follow-up for the composite of cardiovascular death and

heart failure hospitalization was $\approx 15\%$ in DAPA-HF, but $\approx 21\%$ in the EMPEROR-Reduced trial.

Although the two trials enrolled overlapping and complementary patient populations, the two trials reported highly concordant results. The combined risk of cardiovascular death or hospitalization for heart failure was reduced by 25% in each of the two trials, an effect that was highly statistically significant and consistent across pre-defined subgroups. In both trials, this benefit was largely driven by a reduction in the risk of a first hospitalization for heart failure by $\approx 30\%$. These benefits were seen and were of similar magnitude in patients and without diabetes and whether patients were receiving mineralocorticoid receptor antagonists or neprilysin inhibitors. Additionally, both trials reported a meaningful improvement in quality-of-life and excellent tolerability. These striking benefits were seen even though the median duration of follow-up in the two trials (16–18 months) was meaningfully shorter than in the trials with SGLT2 inhibitors in patients with type 2 diabetes (3–4 years).

Both trials reported a lower risk of a composite of clinically important renal events (chronic dialysis, renal transplantation, or the onset of a sustained and profound decrease in renal function) with a 29% risk reduction in DAPA-HF and a 50% risk reduction in EMPEROR-Reduced. The benefit on renal events reached nominal statistical significance in the trial with empagliflozin, but not in the trial with dapagliflozin, Table 1. In contrast, the risk of cardiovascular death was reduced by 18% in the DAPA-HF and by 8% in the EMPEROR-Reduced trial. The benefit was nominally significant in the trial with dapagliflozin but not in the trial with empagliflozin. This variability highlights the difficulties in reaching conclusions when an analysis focuses on non-primary endpoints in an individual trial, especially when the duration of double-blind treatment is short and when the trial was not specifically designed or powered to evaluate a specific effect. If the totality of evidence is ignored, the mortality effect might appear to be greater with dapagliflozin than with empagliflozin in two trials of patients with heart failure and a reduced ejection (with or without type 2 diabetes), whereas the mortality effect might appear to be greater with empagliflozin than with dapagliflozin in two trials of patients with type 2 diabetes (with or without heart failure). When the totality of evidence is considered, the degree of heterogeneity was highly significant in the trials of patients with type 2 diabetes,¹ but no heterogeneity was observed in trials of patients with heart failure and a reduced ejection fraction.¹⁴ This pattern of inconsistency should be expected when the magnitude of the effect size is modest. The risk reduction for all-cause mortality was 15% in the meta-analysis of the trials with type 2 diabetes and in 13% in the meta-analysis of the trials of heart failure with a reduced ejection fraction.^{1,14}

Conclusions

The totality of evidence from two large-scale randomized placebo-controlled trials (considered together with the findings in trials in type 2 diabetes) demonstrates a strikingly consistent effect of SGLT2 inhibition with dapagliflozin and empagliflozin to favourably affect the clinical course of heart failure, including a reduction in major adverse cardiovascular and renal outcomes. These benefits are attained regardless of the presence or absence of diabetes or the use of

Table 1 Effects of dapagliflozin and empagliflozin on heart failure and renal outcomes in trials of patients with type 2 diabetes and in trials of patients with heart failure with a reduced ejection fraction

Trials in type 2 diabetes (with or without heart failure)		
	DECLARE-TIMI58 (dapagliflozin)	EMPA-REG OUTCOME (empagliflozin)
Cardiovascular death or hospitalization for heart failure	0.83 (0.73–0.95) [913 events]	0.66 (0.55–0.79) [463 events]
First hospitalization for heart failure	0.73 (0.61–0.88) [498 events]	0.65 (0.50–0.85) [221 events]
Renal composite endpoint	0.53 (0.43–0.66) [365 events]	0.54 (0.40–0.75) [152 events]
Cardiovascular death (all randomized patients)	0.98 (0.82–1.17) [494 events]	0.62 (0.49–0.77) [309 events]
Cardiovascular death (patients with prior myocardial infarction) in pa	0.92 (0.69–1.23) [183 events]	0.59 (0.44–0.79) [183 events]
Trials in heart failure and a reduced ejection fraction (with or without diabetes)		
	DAPA-HF (dapagliflozin)	EMPEROR-Reduced (empagliflozin)
Cardiovascular death or hospitalization for heart failure	0.75 (0.65–0.85) [877 events]	0.75 (0.65–0.86) [823 events]
First hospitalization for heart failure	0.70 (0.59–0.83) [549 events]	0.69 (0.59–0.81) [588 events]
Renal composite endpoint	0.71 (0.44–1.16) [67 events]	0.50 (0.32–0.77) [88 events]
Cardiovascular death (all randomized patients)	0.82 (0.69–0.98) [500 events]	0.92 (0.75–1.12) [389 events]

Treatment effects are shown as hazard ratios and 95% confidence intervals for the comparison of the SGLT2 inhibitor and placebo, along with the number of events across the two treatment groups which contributed to the analysis. The definition of serious adverse renal events varied somewhat from the trial to trial, but typically included the need for chronic dialysis or renal transplantation or a sustained and profound decline in glomerular filtration rate. Two different analyses are provided for the analysis of cardiovascular death in the two trials in patients with type 2 diabetes; the analysis in patients with a prior myocardial infarction is provided to ensure comparability of the patient cohorts in the two trials.

SGLT2, sodium–glucose co-transporter-2.

mineralocorticoid receptor antagonists and neprilysin inhibitors. These favourable effects can be achieved by drugs that can be given once daily and do not require uptitration, and their use is not accompanied by hypotension, bradycardia, hyperkalaemia, or azotaemia, concerns that often accompany the use of currently recommended treatments for heart failure. This remarkable replication supports the role of dapagliflozin and empagliflozin as a new standard of care for patients with heart failure and a reduced ejection fraction.

Conflict of interest: The authors of this paper were members of the Executive Committee for the EMPEROR-Reduced trial with empagliflozin, which was sponsored by Boehringer Ingelheim and Eli Lilly and Company. M.P. has consulted for Abbott, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. J.B. has received research support from the National Institutes of Health, Patient-Centred Outcomes Research and the European Union, and he has served as a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, LinaNova, Luitpold, Medtronic,

Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, V-Wave Limited, and Vifor. G.F. has consulted for Boehringer Ingelheim, Novartis, Vifor, Servier, Medtronic and received lecture fees from Merck. S.D.A. has recently received fees for steering committee activity, advisory board work, and/or speaking from AstraZeneca, Bayer, Boehringer, Brahms, Novartis, Respicardia, Servier, and Vifor, and he has received grants for the execution of investigator-initiated trials from Abbott Vascular and Vifor. F.Z. has recently received steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, NovoNordisk, and Vifor Fresenius.

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