Title: A welcome “failure” of gliflozins - blood pressure in heart failure

Comment on: Empagliflozin improves outcomes in heart failure with preserved ejection fraction irrespective of blood pressure: the EMPEROR-Preserved Trial

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SGLT2 inhibitors improve outcomes in heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). Two prospective large randomised trials and ameta-analysis place these drugs as the only therapy to improve outcomes in patients with HFmrEF/HFpEF[1–3]. This is not the end of the success story. To have a meaningful impact, any new drug must be used by physicians and prescribed to patients and not just simply added to guidelines [4]. Several factors play into the prescribing inertia that we are unfortunately all too familiar with in heart failure. These include, but are not limited to, lack of access to drugs, cost, health care systems and regulations and physician hesitancy. Some of this hesitancy stems from perceived lack of benefit in some groups or fear of side effects. In this issue of the European Heart Journal Böhm *et al.* [5] address these two issues with regards to blood pressure in patients enrolled in EMPEROR-Preserved[2].

In this analysis of EMPEROR-Preserved the authors set out to answer two questions. The first was does the efficacy of empagliflozin in HFmrEF/HFpEF vary by blood pressure? This is a simple question but is crucial in a population where hypertension is a common co-morbidity. In EMPEROR-Preserved 90% had a history of hypertension and the mean systolic blood pressure was 132 mmHg[6]. It is conceivable that those with lower blood pressure or higher blood pressure may have a different pathophysiological process that led their heart failure that makes them more or less amenable to SGLT2 inhibition. However, in response to their first question, the EMPEROR-Preserved investigators found that there was no difference in the efficacy of empagliflozin by baseline blood pressure on reducing the primary composite endpoint of cardiovascular death or hospitalisation for heart failure, or first hospitalisation for heart failure alone[5]. Importantly, safety outcomes, including acute

renal failure, volume depletion,hypotension and symptomatic hypotension were not different between the patients randomised to empagliflozin compared to placebo. These findings are reassuring and perhaps to be expected. For health care professionals caring for patients with heart failure, the common issue that arises is the management of low blood pressure that often prevents the use of evidence-based therapies like beta-blockers and ACE inhibitors, angiotensin receptor blockers and sacubitril/valsartan. Therefore, the second question the authors asked, what is the effect of empagliflozin on blood pressure in patients with HFmrEF/HFpEF is perhaps the more important one.

In EMPEROR-Preserved, the effect of empagliflozin on the systolic and diastolic blood pressures followed the same patterns. In patients with a pressure >130mmHg there was a fall in blood pressure while for those with a blood pressure of 110-130mmHg and <110 mmHg there was a rise in blood pressure [5]. This happened in both the placebo and the empagliflozin groups suggesting some regression to the mean. When the placebo changes were accounted for in the analysis and a comparison between the placebo and empagliflozin groups was made, there was a 2-4 mmHg reduction in blood pressure that was not statistically significant different between the groups[5]. Furthermore, there was no difference by two key subgroups, those with and without type 2 diabetes mellitus and left ventricular ejection fraction defined as HFmrEF versus HFpEF. For the practicing clinician these are important findings as they reassure us that the gliflozins can be used without worrying about any significant blood pressure lowering effect. As the prevalence of hypertension in HFmrEF/HFpEF is high, the proportion of patients with a blood pressure <110mmHg was low (8%). However, we have data from multiple trials now and if we compare the

findings of this analysis to those conducted in EMPEROR-Reduced[7], DAPA-HF [8]and DELIVER[9] (Central Figure) we see a consistent message; there is a small reduction in blood pressure with SGLT2 inhibition in the overall populations of the magnitude that is well within the limits of variability of automated blood pressure monitors and much lower than physiological changes that happen in blood pressure with changes in posture[10].

While these data help us to utilise the benefits of SGLT2 inhibitors in clinical practice there are still some issues that remain. All of the trials of SGLT2 inhibitors in heart failure excluded patients with low systolic blood pressure (<100mmHg in the EMPEROR trials, <95mmHg in DELIVER and DAPA-HF) therefore we still do not know what the lower limit of blood pressure is that these drugs can be safely used. The other issue is the use of gliflozins during an episode of decompensation for heart failure as all of these trials were conducted in outpatients (apart from the 654 patients in DELIVER who were enrolled during or within 30 days of a heart failure hospitalisation). There are some data from the EMPULSE trial in 530 patients with de novo or chronic heart failure during an episode of decompensation who were randomised to empagliflozin or placebo[11]. Patients were randomised after at least 24 hours in hospital and had to have a systolic blood pressure of at least 100 mmHg and have had no inotropic support for at least 24 hours, no symptoms of hypotension, and in the 6 hours prior to randomisation no increase in the i.v. diuretic dose and no i.v. vasodilators including nitrates. In the EMPULSE trial there was no change in systolic or diastolic blood pressure at 90 days in the empagliflozin group (change in systolic blood pressure 0.1mmHg (95%CI -2.5 to 2.7 mmHg), diastolic blood pressure −0.3 mmHg (95% CI −1.8 to 1.3)).

The analysis by EMPEROR-Preserved investigators adds further detail to the picture of SGLT2 inhibitors in heart failure[5]. Unusually, we find ourselves welcoming the "failure" of the gliflozins to have an effect. As we have seen in this analysis, and others, it is clear that in patients with heart failure, the SGLT2 inhibitors have no significant clinical effect on blood pressure. We hope that this finding will help reassure clinicians about the remarkable safety profile of these drugs and ultimately lead to more patients receiving these prognosis improving drugs.

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Central Figure

Change in systolic blood pressure in patients with heart failure randomized to empagliflozin (EMPEROR-Reduced and EMPEROR-Preserved) or dapagliflozin (DELIVER and DAPA-HF).