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INVITED EDITORIAL

Sodium–glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction: Treat the heart, cherish the kidney

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This article refers to 'Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: Insights from the EMPEROR-Preserved trial' by A. Sharma *et al.*, published in this issue on pages 1337–1348.

We have known for decades that guideline-recommended medical treatments in heart failure (HF) with reduced ejection fraction (HFrEF) often have an impact on kidney function.[1] Therapies such as angiotensin-converting enzyme inhibitors or mineralocorticoid receptor antagonists induce a small drop in estimated glomerular filtration rate (eGFR), with a yearly decline in eGFR thereafter that is similar to placebo. Despite this initial drop, these therapies improve clinical outcomes in patients with HFrEF.[2]

Until recently, lack of effective therapies for HF with preserved ejection fraction (HFpEF) meant that the drop in eGFR associated with these ineffective treatments did translate in worse outcomes, although this association was not found for all therapies.[2] Now that we have multiple studies to show effectiveness of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in improving clinical outcome (especially HF events) in patients with HFpEF, also the renal effects in this particular patient cohort deserve attention. In the current issue of the Journal, Sharma and colleagues provide information on this subject in the EMPEROR-Preserved study cohort.[3]

First, it is important to notice that in both large scale randomized controlled trials with SGLT2i in patients with HFpEF (DELIVER and EMPEROR-Preserved) patients were excluded if the baseline eGFR was either lower than 25 or 20 ml/min/1.73 m^2, respectively.[3,4] In both studies, the prevalence of chronic kidney disease (CKD) (eGFR <60 ml/min/1.73 m^2) was around 50%. SGLT2i improved HF-related events in both trials, and in patients with and without CKD at baseline.

The most interesting information comes from the analyses of the slope in eGFR with either placebo or SGLT2i. Even the long-term natural slope in eGFR in patients included in both trials deserves some attention, as not much is known about this in this HF phenotype.[3,5] Typically, eGFR drops around 0.5–1.0 ml/min/1.73 m^2/year in healthy individuals throughout their lifetime.[6] Patients with severe CKD can have a drop up to 5 ml/min/1.73 m^2/year or even greater, depending on underlying cause. We know from SGLT2i and angiotensin receptor–neprilysin inhibitor trials that in HFrEF the eGFR slope without SGLT2i is −2 to −3 ml/min/1.73 m^2/year.[7,8] When we compare this with data in HFpEF, the slope in the placebo group of DELIVER was significantly more shallow (−1.5 ml/min/1.73 m^2/year), while in the current analysis from EMPEROR-Preserved this change in eGFR was more in line with HFrEF data (−2.6 ml/min/1.73 m^2/year).[3,5] As the authors noted, SGLT2i attenuated the drop in eGFR also in HFpEF by 1.0 ml/min/1.73 m^2/year in EMPEROR-Preserved and by 0.5 ml/min/1.73 m^2/year in DELIVER. We do not fully understand (i) the reason for the initial drop in eGFR with SGLT2i, and (ii) why SGLT2i significantly modify the slope in eGFR in HF, CKD, or patients with diabetes.[9] It is most important to realize that the drop in eGFR is not the result of loss of nephrons, but probably related to changes in intraglomerular haemodynamics, considering the reversible nature. However, without proper renal haemodynamic studies in HFpEF patients, this remains speculation. In contrast, the drop in eGFR observed with placebo probably is related to nephron loss and worsening HF status. Therefore, even though there is no other way of presenting this, slopes in eGFR depicting an active treatment (that impacts eGFR) and placebo together, actually represent two entirely different pathophysiological entities. We also must acknowledge that the effect of SGLT2i on the slope in eGFR over time in both DELIVER and EMPEROR-Preserved was smaller than observed in DAPA-HF and EMPEROR-Reduced.[7,10] Considering also the lower number of events during follow-up, this probably is a reflection of the severity of the HF condition that fitted within the inclusion and exclusion

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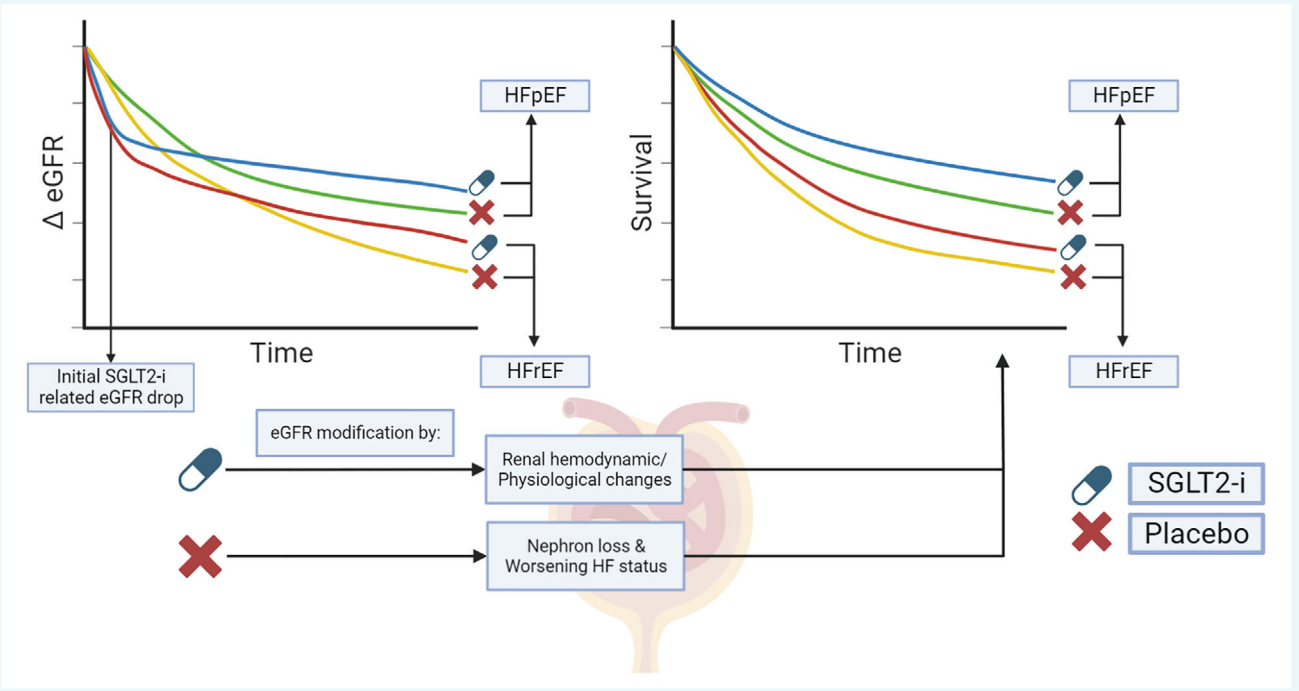

Figure 1 Conceptual overview on renal effect of sodium–glucose cotransporter 2 inhibitors (SGLT2-i) in different phenotypes of heart failure (HF). eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. Created with BioRender.com.

criteria, which seems to be less severe in the HFpEF SGLT2i trials (*Figure 1*).

By whatever analysis you look at the data, either from a kidney perspective or HF perspective, also in patients with HFpEF, SGLT2i reduce the risk of incident HF events, and do so irrespective of the severity of pre-existing CKD or the mentioned drop in eGFR. Some even argue that part of the effect on clinical outcome is actually causatively related to the drop in eGFR, as for instance in DAPA-HF the initial drop in eGFR was a strong effect modifier of the subsequent effect of SGLT2i.[11] It is of vital importance to stress, as many have done before, that a small drop in eGFR during initiation of SGLT2i in patients with HFpEF is expected, and should not be a cause of concern.

So what should we learn from these findings?

These data from EMPEROR-Preserved complete the data on cardiorenal effects of SGLT2i in HF patients with different phenotypes, with and without CKD. If anything, it reinforces the observation that these drugs are safe from a renal and HF perspective and improve renal and HF endpoints even in a heterogeneous HF phenotype such as HFpEF.

Overall, SGLT2i are used to treat the heart in patients with HF, but also cherish the kidney.

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