A mechanistic rationale for the investigation of SGLT2 inhibitors in HFP EF -
Letter regarding the article 'Baseline Characteristics of Patients with Heart
Failure with Preserved Ejection Fraction in the EMPEROR-Preserved Trial'.

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Dear Editor,

recently in this journal Anker et al. published the trial design and baseline characteristics of
the EMPEROR-Preserved Trial.¹ ² Compared to previous HFP EF-trials investigating
established drugs for the treatment of heart failure with reduced ejection fraction (HFrEF), the
mechanistic evidence of empagliflozin as a rationale for treating patients with heart failure
with preserved ejection fraction (HFP EF) seems to be more promising. Accordingly, we
believe that the first experimental findings in human HFrEF and HFP EF myocardium have to
be taken in consideration in this elegant clinical trial as they pave the way for a deeper
mechanistic understanding of potential effects of empagliflozin in the EMPEROR-Preserved
trial.

In this journal³, we firstly demonstrated that empagliflozin has direct diabetes-independent
cardiac effects in human explanted hearts and biopsies. In human myocardium from patients
with HFrEF empagliflozin reduced diastolic dysfunction without altering systolic force. Importantly, this could be expanded to human myocardium from patients with HFP EF by
demonstrating that empagliflozin lowers the typical pathological diastolic stiffness due to
improved titin phosphorylation and other small myofilamentary proteins.³ In a further study,
we showed that these direct cardiac effects are mediated by a reduction of myocardial
inflammation and oxidative stress upon empagliflozin in human HFP EF myocardium leading
to a reduced myofilament stiffness.⁴
The heterogeneity among HFpEF patients is high and previous trials failed to provide prognostic relevant treatment options for HFpEF patients. However, we noted that in the EMPEROR-Preserved trial the number of patients with comorbidities associated with inflammation and oxidative stress (i.e. diabetes mellitus, chronic kidney disease) is higher compared to previous HFpEF trials. Our translational human in-vitro data indicate that empagliflozin might be useful to specifically target these mechanisms in the myocardium of HFpEF patients and may therefore improve diastolic function. Utilizing human hearts with the disease of question is necessary to overcome the limitations of animal models. These translational aspects should be considered for the rationale of the EMPEROR-Preserved trial.

We wish the trialists every success and hope that this study will reveal a new therapeutic option for a mechanistic treatment of HFpEF patients.

References


