LETTERS TO THE EDITOR

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A mechanistic rationale for the investigation of sodium–glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction. Letter regarding the article 'Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial'

Recently in this Journal Anker *et al.* published the trial design and baseline characteristics of the EMPEROR-Preserved trial.[1,2] Compared to previous heart failure with preserved ejection fraction (HFpEF) 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 HFpEF seems to be more promising. Accordingly, we believe that the first experimental findings in human HFrEF and HFpEF myocardium have to be taken into consideration in this elegant clinical trial as they pave the way for a deeper mechanistic understanding of the potential effects of empagliflozin in the EMPEROR-Preserved trial.

In this Journal,[3] 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 HFpEF by demonstrating that empagliflozin lowers the typical pathological diastolic stiffness due to improved phosphorylation of titin 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 in human HFpEF 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.[2] 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.

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