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INVITED EDITORIAL

Plausible effects of sodium-glucose cotransporter-2 inhibitors on adverse cardiac remodelling

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This editorial refers to 'Effect of sodium-glucose cotransporter-2 inhibitors on cardiac remodeling: a systematic review and meta-analysis', by N. Zhang *et al.* doi:10.1093/eurjpc/zwab173.

Adverse cardiac remodelling (ACR) is a common characteristic of abnormalities of cardiac structure and functions, which are a result of natural evolution of numerous cardiovascular (CV) disease and other conditions, such as type 2 diabetes mellitus (T2DM).[1] The pathogenesis of ACR is complex and closely relates to the occurrence of heart failure (HF).[2,3]

During the last decades, ACR has been considering a target for HF point-of-care, while the most dramatic benefits regarding a reversion of impaired cardiac structure and altered function appeared after implementation in routine clinical practice four-component optimal HF therapy including sodium-glucose cotransporter 2 (SGLT2) inhibitor.[4] Although SGLT2 inhibitors sufficiently improved CV outcomes in patients with T2DM with or without HF, the exact molecular mechanisms by which they interfered in nature evolution of ACR and HF remains uncertain.[5] Moreover, it has not clear, whether SGLT2 inhibitors improved HF-related outcomes through a reversion of ACR.[6]

The study by Zhang *et al.*[7] published in this issue of the *European Journal of Preventive Cardiology* has provided a meta-analysis of 13 randomized clinical trials dedicated to an impact of four SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, and luseogliflozin) on ACR in patients with T2DM having or not having HF. The study population consisted of 1251 patients with T2DM, in which the beneficial effects of SGLT2 inhibitors on a wide range of cardiac characteristics [left ventricular (LV) ejection fraction (LVEF), LV mass, LV mass index, LV end-systolic volume, LV end-systolic volume index, and E-wave deceleration time] were found. The analysis in subgroups has yielded that SGLT2 inhibitors have demonstrated the cardiac protective effects mentioned above solely in patients having HF regardless of their glycaemic status. In addition, the most prominent alleviation of ACR was established in individuals who had HF with reduced ejection fraction (HFrEF) and those who were treated with empagliflozin when compared with other SGLT2 inhibitors. The authors concluded that the significant reversion of ACR in HFrEF patients was a remarkable attribute of innate capabilities of empagliflozin, which is considered being more beneficial than other SGLT2 inhibitors for HF patients independently from their glycaemic status.

The main benefit of the results received in the study for readers is undoubtedly strong evidence of ACR reversibility during SGLT2 inhibition that deserve to be considered.

However, there are several methodological issues and limitations, which require thoroughly elucidation.

First, the meta-analysis included studies, for which ACR was not in the focus as a primary end-point. Four clinical studies (SUGAR-DM-HF, EMPA-TROPISM, REFORM, and DAPACARD) from 13 trials have been specifically designed as having magnetic resonance imaging main-study or pre-specified echocardiographic sub-study. Other studies that were included in the study focused on both clinical outcomes and cardiac remodelling characteristics. Undoubtedly, it substantially increased heterogeneity of the pooled data, although the methodology of the meta-analysis did not exert an impact on the final interpretation of the results.

Secondary, authors have minimized heterogeneity in the overall results of cardiac remodelling characteristics by removing the EMPA-TROPISM (ATRU-4) study in which were selected non-T2DM patients having HFrEF. It appeared to be effective approach without diminishing overall result of the study. However, between-studies heterogeneity remained to be respectively high due to a use of both echocardiographic and cardiac magnetic resonance imaging characteristics for ACR.

Third, the number of T2DM patients with HF with preserved ejection fraction (HFpEF) was limited in the study, and consequently, authors did not received significant outcomes in this subgroup, while they had expected. It is becoming clear that new studies to elucidate the role of SGLT2 inhibition on ARC in HFpEF require being planned.

There at least two meta-analyses, which have previously demonstrated controversial issues for SGLT2 inhibition on cardiac

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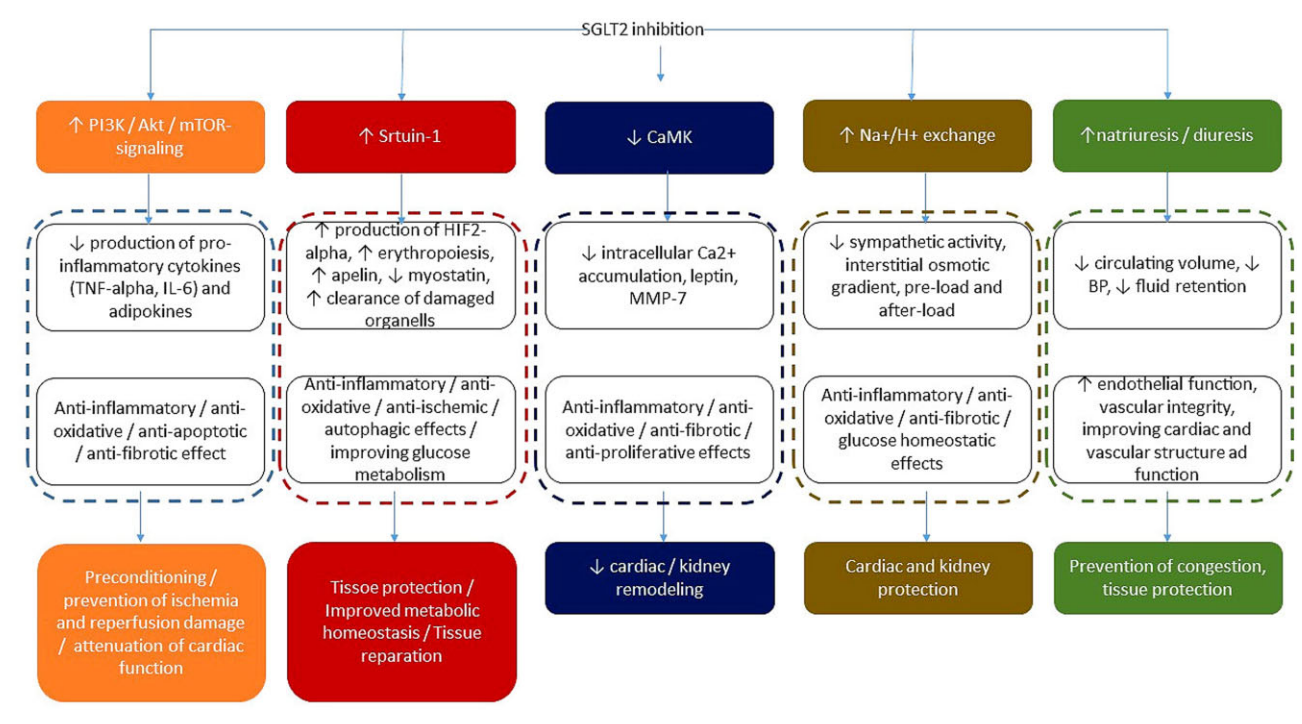

Figure 1 Plausible mechanisms of tissue protection of sodium-glucose cotransporter 2 inhibitors. Akt, serine/threonine-specific protein kinase; BP, blood pressure; CaMK, Ca2+/calmodulin-dependent protein kinase; MMP, matrix metalloproteinase; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin.

protection and reversibility of ACR.[8,9] Yu *et al.*[8] found that SGLT2 inhibitors in T2DM patients seem not to show substantial effects on cardiac structural parameters, while they appeared to be significantly effective on LVEF increase solely in patients with HFrEF. Another meta-analysis of five randomized clinical trials has compared the effects of SGLT2 inhibitors and placebo on conventional parameters reflecting ACR.[9] The authors reported that SGLT2 inhibitors leaded to more prominent regression of LV mass, but not LV mass index, when compared with placebo, while analysis in subgroups did not show a significant difference in these parameters depending on phenotype of HF and presence of T2DM. Thus, Zhang *et al.*[7] giving strong evidence for superiority of empagliflozin to other SGLT2 inhibitors on the reversion of ACR have to be congratulated for this coherent issue.

Admittedly, findings received by Zhang *et al.*[7] seem to be valued for routine clinical practice because they open out new perspectives for the T2DM/non-T2DM patients with HFrEF and probably for those who had HF with mildly reduced and preserved ejection fraction. Current European Cardiology Society clinical guideline for the diagnosis and treatment of acute and chronic HF has pointed out new indications for SGLT2 inhibitors, but only two SGLT2 inhibitors (dapagliflozin or empagliflozin) were recommended for HFrEF patients, while significantly more agents have been incorporated into the care of T2DM patients at the risk of HF.[10] Obviously, the weakness is a lack of the direct comparisons between these drugs. The last, but not least, new medical approach will have an intriguing clinical decision in *de novo* acute HF/chronic HF among post-ST-segment elevation myocardial infarction or acute myocarditis/post-myocarditis patients having as it is expecting good perspectives for restoration of a global cardiac function, declining all-cause mortality, CV mortality, and HF re-admission.

Favourable pleiotropic effects of SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, and luseogliflozin) on ACR were superior to placebo in T2DM patients with and without HF. However, it remains unclear by which molecular mechanisms these agents, especially empagliflozin, yield a specific potency in term of improvement of cardiac performances (see *Figure 1*). Large clinical trials with face-to-face comparison of different SGLT2 inhibitors require clearly elucidating their activity in the future.

Conflict of interests: none declared.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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