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Reply to SGLT-2 inhibitors: Post-infarction interventional effects

Dear Sir,

I would like to thank you and your team for being interested in our article. As highlighted, our study is the first registry investigating the in-hospital and long-term outcomes in patients with type 2 diabetes mellitus (T2DM) admitted with acute myocardial infarction (AMI), comparing those under chronic SGLT2-inhibitor (SGLT2-I) treatment versus non-SGLT2-I users. The use of SGLT2-I was associated with a lower rate of the composite endpoint of major adverse cardiovascular events (MACEs), cardiovascular mortality, and heart failure (HF) hospitalization compared to non-SGLT2-I users. Moreover, after adjusting for all confounding factors, the use of SGLT2-I was identified as an independent predictor of lower occurrence of MACEs and HF hospitalization [1]. First, we would like to highlight that SGLT2 protein was shown to be present at cardiac level, mainly when cardiac damage occurs [2]. Specifically, several mechanisms have been described to support the beneficial effects of SGLT2-I: i) the improvement of glucose control; ii) the increase in diuresis/natriuresis with decrease in blood pressure; iii) the trigger for the cardiomyocyte "metabolic flexibility", promoting a shift from intracellular glucose to ketone bodies as metabolic substrate, with greater ATP production available for cardiac contraction; vi) anti-inflammatory effect since we demonstrated that the inflammatory indices on admission and after 24 h in T2DM patients with AMI were significantly higher in non-SGLT2-I users compared to the SGLT2-I group; v) reduction of the arrhythmic burden; vi) improvement of sympathetic/parasympathetic nerve activity [3–5]. Thangaraju et al., in their comment, highlighted that the protective effect of SGLT2-I on T2DM patients with AMI might be sustained by additional factors, not necessarily heart-related [6]. They underline that an SGLT2-inhibitor-mediated increase in erythropoietin levels might be a possible further explanation for their pleiotropic beneficial effects [6]. Indeed, Mazer et al. showed that empagliflozin administration was associated with increased erythropoiesis via enhanced erythropoietin secretion by the kidney [7]. This SGLT2-I-mediated increase in erythropoietin production might result in systemic organ protection as a circulating cytokine, potentiating cardiomyocyte mitochondrial function, triggering angiogenesis and cell proliferation, and lowering the inflammatory burden. In addition, an increase in erythropoietin-induced hematocrit may improve myocardial metabolism by enhancing myocardial oxygen delivery. Taking all these points together, we agree that a further potential benefit of SGLT2-I might be the enhanced erythropoietin levels, acting in combination with the other mechanisms listed above. We also agree with Thangaraju et al. that whether SGLT2-Is exhibit a class- or a drug effect remain an unsolved question. In our study, we included 111 patients treated by SGLT2 inhibitors (most of them by empagliflozin), but the sample size was powered to evaluate only a "class effect" and not the "doses effect" [1]. However, a recent analysis of a nationwide real-world dataset suggested that the risk of cardiovascular events, including HF, myocardial infarction, stroke, and atrial fibrillation, would be comparable between individual SGLT2-I, supporting our hypothesis of "class effects".

Ethics approval and consent to participate

Data were collected as part of an approved international multicenter observational study. The present study was conducted according to the principles of the Declaration of Helsinki; all patients were informed about their participation in the registry and provided informed consent for the anonymous publication of scientific data.

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Author contributions

PP and LB contributed conception and design of the study; PP, LB, AC, NM, FG, MA, AS, AS, GE and AI organised the database and collected data; LB and EG performed the statistical analysis; PP and LB wrote the first draft of the manuscript; FG and AC wrote sections of the manuscript. GS, CS, AF, GC, CM, RM, NM, JAO, DV, PC, EB and CP revised the article and approved the final version of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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none.

Competing interests

The authors declare that they have no competing interests.

Statement of guarantor

C.P. and E.B. are the guarantors of the research and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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