

Answers to Reviewers

Reviewer #1

The authors must be complimented for selecting a crucial but lesser understood topic, for a review. The efforts for the review are thorough and commendable. A few aspects may be further considered, for giving a more holistic understanding, based on the current knowledge.

[We thank this reviewer for his encouragements and approval.](#)

Reviewer #2

Evaluation of the paper 77326 A review of potential mechanisms and uses of SGLT2 inhibitors in ischemia-reperfusion phenomena. The aim of the study was to summarize evidence which associate SGLT2i and ischemia/reperfusion injuries, by first listing known mechanisms which portend the latter, and second, hypothesize how the former may interact with these mechanisms. The authors conclude that beyond the cardiovascular benefits observed in patients with chronic heart failure treated by SGLT2i, data from large clinical trials including EMPA-REG or DAPA-HF may suggest a benefit through ischemia-reperfusion events. The inhibition of the Na⁺/H⁺ exchanger may play a pivotal role in such cardioprotective feature and further investigations towards the immunomodulatory properties of SGLT2i drug-class are warranted. Comments 1. This is a well written paper with a theory of the way action of SGLT2i and induction of clinical benefit. 2. The text and the figures are satisfactory and informative. 3. References are up-to-date, however the following reference might improve the paper: - Zurbier CJ. Does acute treatment of dapagliflozin reduce cardiac infarct size through direct cardiac effects or reductions in blood glucose levels? *Cardiovasc Diabetol.* 2020 Sep 19;19(1):141. - Tanajak P, Sa-Nguanmoo P, Sivasinprasasn S, Thummasorn S, Siri-Angkul N, Chattipakorn SC, Chattipakorn N. Cardioprotection of dapagliflozin and vildagliptin in rats with cardiac ischemia-reperfusion injury. *J Endocrinol.* 2018 Feb;236(2):69-84. 4. The conclusions of the paper has practical implications.

[We thank this reviewer for his critics. Both these references were added to the manuscript.](#)