

## **Response to Reviewer's comments:**

### **Reviewer #1:**

**Q1** There is no mention of MACE in the whole editorial which is quite surprising as we are discussing the cardiovascular benefits of SGLT2 inhibitors in the context of various CVOT.

**Response:** Thank you very much for your review with valuable suggestions. We greatly appreciate the time you have contributed to the review process.

We have added the references regarding MACE benefits of SGLT2 inhibitors.

4 Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020; 396: 819-829 [PMID: 32877652 DOI: 10.1016/S0140-6736(20)31824-9]

5 Rossing P, Inzucchi SE, Vart P, Jongs N, Docherty KF, Jhund PS, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, DeMets DL, Bengtsson O, Lindberg M, Langkilde AM, Sjöstrand M, Stefansson BV, Karlsson C, Chertow GM, Hou FF, Correa-Rotter R, Toto RD, Wheeler DC, McMurray J, Heerspink H. Dapagliflozin and new-onset type 2 diabetes in patients with chronic kidney disease or heart failure: pooled analysis of the DAPA-CKD and DAPA-HF trials. *Lancet Diabetes Endocrinol* 2022; 10: 24-34 [PMID: 34856173 DOI: 10.1016/S2213-8587(21)00295-3]

6 McMurray J, Solomon SD, Docherty KF, Jhund PS. The Dapagliflozin and Prevention of Adverse outcomes in Heart Failure trial (DAPA-HF) in context. *Eur Heart J* 2021; 42: 1199-1202 [PMID: 31898736 DOI: 10.1093/eurheartj/ehz916]

7 Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray J, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet* 2020; 396: 121-128 [PMID: 32446323 DOI: 10.1016/S0140-6736(20)30748-0]

8 McMurray J, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozd J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman C, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; 381: 1995-2008 [PMID: 31535829 DOI: 10.1056/NEJMoa1911303]

9 Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; 383: 1413-1424 [PMID: 32865377 DOI: 10.1056/NEJMoa2022190]

**Q2** There are lot of abbreviations mentioned like AMPK/PGC-1alpha proteins, MYPT1 etc which need full forms for the reader's convenience.

**Response:** We have added the full forms for abbreviations.

**Q3** More elaborations of the pathways involved in the cardiovascular benefits of SGLT2 inhibitors is needed. There are many grammatical and spelling mistakes which need correction.

**Response:** We have carefully checked and revised grammatical and spelling mistakes

**Reviewer #2:**

*the manuscript is about a novel idea and an interesting but, it lacks clarity of methodology in both the abstract and in the body. in addition, the results are not well-written*

**Response:** Thank you very much for your review with valuable suggestions. We greatly appreciate the time you have contributed to the review process.

We understand your concerns regarding the perceived lack of clarity in the methodology and the presentation of results. As this manuscript is an editorial, it follows a narrative style that is inherently different from research articles. However, we acknowledge that clarity is paramount in conveying our novel ideas effectively. To address your concerns, have made some revision.