ROUND 1

The authors of manuscript ID 78556 sincerely thank the reviewers for taking their time to provide detail feedback regarding aspects of the manuscript that require improvement. We have worked diligently to address the feedback to the best of our abilities. Please see below.

Response to Reviewer 1:
Comment 1: Confusion regarding the definition of MetS per the NCEP ATP III criteria.

Response: We agree with the reviewer. We have clarified this is the manuscript and it reads this: "The primary aim of this study is to evaluate the impact of the SGLT-2 inhibitors on the MetS parameters noted in NCEP ATP III criteria. The secondary aim is to highlight the effect of SGLT-2Is on other cardiometabolic parameters including hemoglobin A1C (HbA1c), body weight (BW) and uric acid (UA)" from line 85-89 in the introduction.

Comment 2: The use of many abbreviations

Response: we agree to this. We have spelled out each abbreviation before repeating them in the manuscript.

Comment 3: Discussion section requires extensive review. Authors should describe, analyze and interpret their main results. They should also explain the significance of their results and bring it back to the research questions and not just replicate what exists in the literature

Response: We believe we have addressed this from lines 209-253 and it reads: *"This meta-analysis of 16 placebo controlled RCTs was designed to primarily evaluate the impact of SGLT-2 inhibitors on the components of the MetS as defined by the NCEP ATP III criteria. In addition, it evaluated their impact on other cardiometabolic parameters including HbA1c, BW and UA. The major findings include: 1) an improvement in MetS components (FPG, WC and BP) in the SGLT-2I group compared to the placebo group and 2) an improvement in HbA1c, BW and UA in the SGLT-2I group compared to the placebo group.*
Previous meta-analyses [40-50] that evaluated the cardiometabolic effects of SGLT2-Is have only included at most four of the five components of MetS. Teo et al [40] evaluated WC, BP, FPG; Cho et al (49) analyzed WC, BP, HDL and Zaccardi et al [47] evaluated FPG, BP, HDL and TGL. In addition, the results of these studies have been inconsistent. While our study aimed to evaluate all components, we only had enough data for four components (FPG, BP, WC and HDL) owing to our inclusion criteria. In

contrast to studies [42] [43] [50], our study did not highlight a significant improvement in HDL with the use of SGLT2-Is. The reason behind this might be an inadequate statistical power; this study analyzed only 3 RCTs owing to the inclusion criteria compared to 47, 5 & 15 RCTs by Sanchez-Garcia et al, Chen et al, and Shi et al respectively [42] [43] [50]. This study also evaluated the effect of low-dose SGLT2-Is on HDL, however it is unlikely this played a role in the outcome as the analysis by Chen et al (49) demonstrated a dose-independent impact. While this study has a higher mean treatment duration of 79 weeks compared to prior meta-analyses which have a mean duration of 29 weeks [40-50], the magnitude of the improvement in FPG, WC and BP appear similar between this study and its counterparts. This might suggest that SGLT2-Is have a ceiling effect on the components of MetS.

A high heterogeneity is noticed across all outcomes except for WC. This could be related to the differences in baseline diabetic medications taken by the patients, different doses, inclusion of more than one type of SGLT-2I and differences in the severity of hyperglycemia among the patients. However, the subgroup analysis for FPG based on dose revealed a significantly elevated heterogeneity with all doses evaluated. This study could not adjust for the differences in baseline diabetic medications and severity of hyperglycemia because these were universally different across the included RCTs, and a patient level meta-analysis would be needed for this. The heterogeneity associated with SBP outcome in the empagliflozin subgroup may be due to the significant difference in sample size between the analyzed RCTs. A further sub analysis based on the sample size was not completed because there were only 2 studies in the empagliflozin subgroup for SBP. The difference in efficacy between both SGLT2-Is on SBP appears to be largely due to the significant difference in the number of RCTs that constitute both SGLT-2I subgroup (2 RCTs in the empagliflozin subgroup versus 5 RCTs in the dapagliflozin subgroup). The small number of RCTs in the empagliflozin subgroup is due to this study's inclusion criteria. The differences between the patients' baseline antihypertensives could also be contributory to the high heterogeneity in the empagliflozin subgroup for SBP. The significant difference in treatment duration between the studies that evaluated DBP might explain the significant heterogeneity. Associated with 10mg dose of dapagliflozin. Inadequate power might explain the lack of statistical significance in the reduction of DBP" and from lines 271-300 and it reads: "*Perhaps through the improvement in MetS components, the combination of the above mechanisms might explain the improvement in CV mortality and HF hospitalization associated with SGLT2-Is in landmark trials [1-4,6,7,9-13]. In addition to its role in CVD, MetS is an independent risk factor in the development of DM [56,57]. Patients with MetS are approximately three to five times more likely to develop type 2 DM [56,57]. Interestingly, while the risk is lower, it is independent of the presence of elevated FPG [56]. This highlights the complex yet*

incompletely understood connection between MetS, type 2 DM and CVD. Although the improvement in MetS components in this study appears to be modest, our findings anticipate a possible role for SGLT2-Is in the management of MetS. Hence, it highlights the need for RCTs to evaluate the impact of SGLT2-Is on MetS compared with current management modalities including lifestyle modification.

Limitations

The findings of this study should be interpreted cautiously bearing several limitations. First, the mean baseline HDL and DBP of included RCTs did not meet threshold values for MetS. This is likely because our primary objective was mostly a derivative of the secondary outcomes of the included RCTs. Second, owing to our inclusion criteria, only two of the included RCTs recruited patients without DM which limits the external validity of our study. Furthermore, we did not conduct a patient level analysis in those without DM. Third, this study limited its analysis to only dapagliflozin or empagliflozin and did not thoroughly compare the efficacy of both. Fourth, the improvement in MetS components noted by our analysis might be confounded by other medications taken by the RCTs' participants. Therefore, our analysis could not quantify the absolute effect of SGLT2-Is. This might imply the need for the evaluation of SGLT2-Is as a first line pharmacotherapy in treatment of MetS components. Additionally, MetS has multiple causes besides sedentary lifestyle, and unhealthy eating; it is usually heterogenous in its presentation due to the different possible combinations of its components; this study did not address these in its analysis. Lastly, not all included RCTs are open labelled and hence the risk of bias could not be reliably assessed by the Cochrane risk of bias tool"

Comment 4: Abstract ¬ Line 33 – cardiovascular disease (CVD) or cardiovascular (CV) disease.

Response: We agree, and we have used the CVD abbreviation throughout the manuscript

Comment 5: Please change. ¬ Line 35 – DM. Please add the full name

Response: We agree and have spelled this as diabetes mellitus before using the 'DM' abbreviation.

Comment 6: Please provide information about the retained randomized controlled trials in the methods section

Response: We have provided this in the method section (Study selection subsection) and it reads: *"The eligible studies were RCTs, allocated patients to an SGLT2-I group (that received either Dapagliflozin or Empagliflozin) or a placebo group, reported baseline and post-treatment values ≥1 component of MetS, had a treatment duration 6 months and were published in the English language. Studies not meeting these criteria were excluded. Disagreements on study selection were either resolved by consensus or by Farouk Mookadam. The study adhered to the preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [22] (PRISMA checklist)" We have also summarized this in figure 1 (the PRISMA flow diagram)*

Comment 7: Please include the analyses conducted on the data in the methods section

Response: *"We have done this in the 'Data analysis' subsection of the method section and it reads: All outcome data were reported as mean with standard deviation and were converted to conventional units. Data analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). The forest plots of the above outcomes were visually represented after pooling the mean differences using the random-effects model. Heterogeneity was assessed with the I^2 test. Post-hoc subgroup analyses including doses and/or SGLT-2I type were performed if there was significant heterogeneity"*

Comment 8: Lines 63-65 – Please add reference

Response: We do not have reference/citation for this because this was a conclusion from the literature search that we conducted.

Comment 9: Line 67 – Table 1? I can't find it in the manuscript. In my opinion, it is best to summarize the definition of MetS in a few sentences. In addition, there are several different definitions of MetS, leading to considerable confusion as to whether they identify the same individuals or represent a proxy for risk factors. A number of factors other than those traditionally used to define MetS that are related to the syndrome were also identified (Kassi et al., 2011). The authors should give readers a brief explanation of MetS and all the components used to define it.

Response: We have addressed this towards the end of the introduction and it reads: *"It has been defined according to the NCEP (National Cholesterol Education Program) ATP (Adult Treatment Panel) III as the presence of 3 of 5 entities: 1) waist circumference (WC) ≥102 cm in men and ≥88cm in females, 2) serum triglycerides (TGL) ≥150 mg/dL or on drug treatment for hypertriglyceridemia, 3) serum high-density lipoprotein (HDL) <40 mg/dL in males and <50 mg/dL, 4) blood pressure (BP) ≥130/85 mmHg or on drug treatment for hypertension (HTN), 5) fasting plasma glucose (FPG) ≥100 mg/dL or on drug treatment for elevated blood glucose [20]….The primary aim of this study is to evaluate the impact of the SGLT-2 inhibitors on the MetS parameters noted in NCEP*

ATP III criteria. The secondary aim is to highlight the effect of SGLT-2Is on other cardiometabolic parameters including hemoglobin A1C (HbA1c), body weight (BW) and uric acid (UA)" We have also decided not to represent the definition of MetS in a table.

Comment 10: Please briefly describe all steps taken until the final list of studies is obtained. Please insert the flow chart in the manuscript.

Response: We have described this briefly in the method section, provided the database search details in the supplemental file and the PRISMA flow chart is in the figure file and labelled as 'figure 1'

Comment 11: Please move the names of the authors from the text to the "Author Contributions"

Response: We agree and have this.

Comment 12: Line 97- FM: You mean Farouk Mookadam?
Response: Yes, FM has been spelled out

Comment 13: Lines 102-106 – Each abbreviation must be mentioned the first time the full name appears in the text.

Response: We have done this

Comment 14: Line 105 – "All outcome data were reported as mean with standard deviation and were converted to conventional units" Please move it to the Data Analysis section.

Response: This has been done, please see the Data analysis subsection of the method section

Comment 15: Line 107 – Quality Assessment: To assess the quality of open-label randomized controlled trials, the use of the Jadad standard is not recommended and the Cochrane risk of bias tool was considered more appropriate (Ma et al., 2012). The authors did not indicate whether or not this type of RCT was evaluated; if so, they should at least mention it as a limitation of the study.

Response: We agree. However, we used the JADAD standard because not all included RCTs were open labelled. We have included that under the limitation subsection in the discussion section and it reads: *"Lastly, not all included RCTs are open labelled and hence the risk of bias could not be reliably assessed by the Cochrane risk of bias tool"*

Comment 16: Please and "and" before BP
Response: We have corrected this

Comment 17: Search results and study inclusion: Please move this paragraph to the "Methods" section.

Response: We sincerely appreciate the reviewers input here, however with all due respect, we do not believe the search results should be included under the 'method' section. Universally, search results for meta-analyses are included in the 'results' section

Comment 18: Figure 1? I can't find it in the manuscript.
Response: We agree and have made sure all figures are correctly labelled and are included in the '78556 Figure file'

Comment 19: Lines 129-130 – Of these, 3 studies reported WC…….... Please add the reference numbers of these studies.

Response: We have done this and it now reads: *Of these, 3 studies reported WC [30] [33] [36], 9 reported FPG [24] [26] [27] [29] [30] [34-36] [39], 4 reported TGL [5] [30] [35] [38], 3 reported HDL [34] [37] [38], 7 reported SBP [12] [15] [28] [29] [33] [35] [36] and 6 reported DBP [24] [26] [28] [33] [35] [39]*

Comment 20: Line 133 – Please add the number of participants in each study (smallest - largest). ¬ Line 137 – Same remark as above (short duration - long duration). ¬ Line 138 – Same remark for age.

Response: These have been included in the Tables summarizing the results in the "78556 Figure file"

Comment 21: Line 174 – TGL is commonly used as a biomarker for MetS. Do the authors have an explanation for the absence of data regarding this parameter?

Response: We have explained this in the result section and it reads: *"TGL levels pre or post treatment were not reported in all the trials. Hence this component of the MetS could not be analyzed in this meta-analysis"*

Comment 22: HbA1C and UA are among the MetS biomarkers, but as far as body weight is concerned, I don't think so. Please justify your choice.

Response: We agree. However, HbA1C and UA were not included in the NCEP ATP III criteria. We analyzed body weight as a parameter of interest because it also correlates with the development of cardiovascular diseases, and it was reported by majority of the RCTs.

Comment 23: Lines 209 – In contrast to other studies [43] [44] [51]…... Please delate "other"
Response: done

Comment 24: Lines 235-256 - This is a simple citation of what exists in the literature. The authors should limit themselves to discussing their main findings.

Response: We agree. However we have briefly described the mechanism of action of SGLT-2Is in an attempt to explain why it is beneficial in patients with MetS.

Reviewer 2:
Comment: The major concern is the fact that MetS is regarded by the Authors as one homogenous feature. In my understanding, this is not the case as the metabolic syndrome accompanies various medical conditions, including medications' side-effects. Threfore one should rather consider the MetS as a heterogenous entity. This raises the question why the treatment with flozines was introduced to all patients? It is hard to believe that numerous patients included it the studies cited were diagnosed with the same disease and therefore treated with only two medications. For instance, the CV diseases include many different conditions. Thus, the suggestion is to describe in detail the groups of patients included in studies which underwent the revision.

Response: We absolutely agree with this reviewer. However, the answers to their comments are beyond the scope of this study. Hence, we have highlighted these concerns under the limitation subsection of the discussion section and it reads:
"*Additionally, MetS has multiple causes besides sedentary lifestyle, and unhealthy eating; it is usually heterogenous in its presentation due to the different possible combinations of its components; this study did not address these in its analysis"*

Reviewer 3:
Comment: Some minor concerns are as followed. 1. The Figure a, b, c...could be revised as Figure 1, Figure 2.... 2. The reference style should revise according to the guideline of BPG.

Response: We agree and have made these changes.

ROUND 2

Authors are invited to correct some grammatical errors.