Response to Reviewers:

Dear Dr Koch,

Regarding **"Implementation of medical management and major adverse cardiovascular events in people with peripheral artery disease and diabetes"** (manuscript ID# 62775) submitted to the **World Journal of Diabetes**, the authors would like to thank your editorial team and reviewers for reviewing this manuscript, and for providing feedback for its improvement. The authors have read each comment carefully and made changes in the manuscript text in response to these comments where appropriate. Tracked changes are visible in the revised manuscript text, with a detailed response to each reviewer/editor comment available below.

Reviewer #1

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Evaluating the success of medical therapy in patients with peripheral artery disease (PAD) is paramount in reducing MACE. Authors of this study have designed a simple medical score to help clinicians in this respect. The study shows that PAD medical score could be of use in these patients. Still, I believe there some issues to be dealt with:

1. PAD medical score as used by authors of this study is calculated by giving more or less arbitrarily points for certain ranges in values of LDL, SBP, HbA1C, smoking history, prescribed antiplatelet medication. Do authors of this study think that this arbitrarily system of points can reflect on the success of the prognostic use of PAD medical score? Please elaborate.

   The authors thank the reviewer for these valid comments regarding the design of the PAD-medical score system. The specific criteria chosen for the scoring system was related to the current target risk factors for MACE in people with CVD according to current clinical guidelines. However, as indicated by the reviewer, the intermediate categories and scorings were somewhat arbitrary, though aimed to indicate partial control of risk factors, though whether these are the most appropriate intermediate target levels are unknown. We have added this uncertainty as a limitation, and have provided additional details in the methods on the overall rationale behind the score system used.

2. Why wasn't statin use included in PAD medical score? Statins are known for their pleiotropic effects which go beyond their capacity to lower cholesterol levels. It would've been interesting to examine the effect of statin use on PAD medical score efficacy, though it is evident that short duration of this study might not be the best scenario to reveal these potential non-cholesterol lowering effects of statins.

   Again we thank the author for their valid comment. We however found that as statin use is related to LDL control, including both in the equation for the PAD-medical score is unfortunately problematic, through causing collinearity in the cox regression models used in the analyses. Also, as other agents may be used for LDL control, and as most of the evidence for statins relates to their LDL-lowering effects, we therefore considered LDL control the most appropriate for the scoring system rather than the presence or absence of statins.

3. Can you please elaborate results from Table 2 through which one understands that only smoking abstinence was significantly associated with a lower risk of MACE per unit increase. Why other parameters of PAD medical score do not show this association?

   The primary objective of the study was to examine association between the PAD-medical score with MACE, with the analysis of subcomponents a secondary objective. We therefore wanted to be cautious in overstating these sub-analyses. The reviewer's interpretation of the result is correct however, and we have acknowledged this in the discussion, where the association of a higher PAD-medical score and reduced risk of MACE appeared to be more dependent on the association of smoking abstinence with lower risk of MACE. This has also been added to the limitations.

4. One table with baseline characteristics of the patients should be included (without data regarding its association to PAD medical score). This table might include levels of HbA1C, duration of disease (diabetes, PAD), duration of therapy, gender differences, ethnic differences etc.

   We thank the reviewer for this useful suggestion, and we have added a table (now Table 1) that details the available patient characteristics at entry into the study.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This study aims to evaluate that PAD-medical score is predictive of the incidence of MACE during short-term follow-up in people with PAD and diabetes. The authors concluded that the PAD-medical score provides a simple way to assess implementation of medical management, which may have substantial benefit in reducing MACE. This article is well written and of clinical interest. However, several issues should be improved before the consideration for publication.

1. In Table 1, the data of body mass index and HDL-C are informative to image the patients.
   The authors thank the reviewer for this suggestion. HDL-c has been added to Table 2, though BMI was not routinely measured in patients and is not available to include.

2. The inclusion and exclusion criteria are unclear in this study.
   We thank the reviewer for identifying this lack of clarity in the methods. The first paragraph of the methods has been re-worded and expanded to more clearly describe the inclusion and exclusion criteria for patients in this study.

3. The PAD-medical score was calculated using the data of serum LDL-C, systolic blood pressure, HbA1c, smoking history, and prescription for an anti-platelet medication. However, Hazard ratio of PAD-medical score for the risk of MACE (0.79) is almost the same to smoking abstinence (0.61), one component of PAD-medical score, which suggests that PAD-medical score is not so benefit for the prediction of MACE compared with smoking abstinence. If the authors claim that PAD-medical score is predictive of the incidence of MACE, the comparison with previous score such as Framingham risk score is needed for the novelty and benefit of PAD-medical score.
   We thank the reviewer for this suggestion, which has highlighted that the manuscript requires further description as to why the PAD-medical scoring system was created and the gap it intends to address. As described in the discussion, the Framingham risk score is

used for populations without established CVD, and the SMART-REACH model has weaknesses related to age group inclusion and a lack of HbA1c. There is therefore no other risk calculation tool available that is appropriate for this population, which has been made more clear in the third paragraph of the methods when leading into the reasoning behind the development of the PAD-medical score.

4. The reason why age, sex, ischemic heart disease and stroke were selected as adjustment factors. Body mass index and pharmacotherapy may be more important factors.
   Age, sex, etc. are established risk factors for MACE, whilst the PAD-medical score is designed to look at the impact of pharmacotherapies that align with clinical guidelines on risk factors.

5. The phrase of "Implementation of medical management" is not inappropriate in the Title, because few descriptions were made in the text. The focus is to be PAD-medical score.
   While the authors believe that the PAD-medical score assesses the implementation (or lack thereof) of medical management and the resulting impact on MACE, and serves as an appropriate surrogate term for medical management, we appreciate the suggestion for a clearer title, and have decided to modify the title as suggested to instead read 'Control of modifiable risk factors and major adverse cardiovascular events in people with peripheral artery disease and diabetes'. The abstract and main text has also been revised in the places where 'implementation of medical management' was stated, and instead replaced with text relating to management of modifiable risk factors.

Science Editor

Issues raised:

1. The “Author Contributions” section is missing. Please provide the author contributions;
   The ‘author contributions’ section was available on page 11 under ‘declarations’, but has been moved to the title page and re-formatted to align with the journal’s requirements.

2. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);
   The approved grant application form has been uploaded as requested.

3. PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;
   The PMID and DOI numbers, and the names of all authors have been added to each reference. The journal name has also been italicized as per the journal’s requirements.

4. The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text; and
   The authors apologise for this omission. An article highlights section has been added at the end of the main text in line with the journal’s requirements.

5. Authors should not cite their own unrelated published articles. Please check and remove any references not relevant to this study.

   We acknowledge that a large number of self-citations can be a point of concern in academia. However, the first author for this manuscript is a top global researcher in the field of Peripheral Artery Disease (PAD), including authorship on an international clinical guideline for PAD, diagnostic guidelines, and several medical management articles. It is therefore difficult to relate the current manuscript to the wider field of research without acknowledging previous research by the authors.