World Journal of Cardiology
Manuscript #33294
Column: Minireviews
Title: Peripheral Interventions and Antiplatelet Therapy: Where Do We Stand in an Era of Guideline Based Therapy?

Response to Reviewers

Reviewer 1:

Paper is well written. Data is summarized very well. For readers understanding well, authors should summarize all clinical trials used in the manuscript. Many clinical trials were not in the table, which made hard to follow the context (i.e Goodney et al, BASIL, BEST-CLI, ESPRIT, PLATO, THEMIS trials etc).

Response:
Thank you for your kind comments. We have added the following trials to the tables (and text) based on recently published information: PAD sub-analyses of PLATO and PEGASUS-TIMI 54, meta-analysis by Thompson et al (studied Cilostazol) as well as early released results for the COMPASS trial. We chose not to include the Goodney publication and the BASIL paper since they are not antiplatelet trials. The BEST-CLI and THEMIS trials are not completed yet so we provided the trial design only in the text. Finally, the ESPRIT trial was conducted in a post CVA/TIA population looking at global vascular events, not specific PAD outcomes.

Reviewer 2:

This review manuscript by Singh et al. is well-written.

Response:
Thank you for your kind comments.

Reviewer 3:

General comments: The manuscript of Singh et al addresses a rather neglected issue of optimal revascularization strategy and anti-platelet therapy in PAD patients. Overall, this manuscript provides a good overview of the studies that were done in PAD patients, either as a subgroup of larger cohorts, or as the main cohort. I am convinced that this paper is both relevant to the field and of interest to the journal audience. However, several changes must be done to improve the manuscript. It would also benefit from additional language editing.

Response:

Thank you for your kind comments. We have attempted to address all of your points with particular focus on language editing.

Detailed comments:
1. Abstract: "Platelet activation and aggregation after percutaneous transluminal angioplasty of atherosclerotic arteries are important risk factors for re-occlusion/restenosis following endovascular procedures". First and foremost, they are a risk factor for life-threatening thrombosis following endovascular procedures. Please modify.

Response:
Corrected.

2. Introduction, p.6: Term "based/basing" is repeated 4 times in 2 sentences. Please edit.

Response:
Corrected.

3. Antiplatelet Therapy, p.6: "antiplatelet therapy in PAD remains largely unstudied as compared to coronary artery disease (CAD) and cerebrovascular disease patients. Multiple antiplatelet agents have been studied in the PAD population, including aspirin, the combination of aspirin and dipyridamole, clopidogrel, ticagrelor, cilostazol and vorapaxar" These two sentences should be rewritten as they seem to convey a contrdicictory message: Therapy in PAD remains unstudied, but multiple agent have been studied in PAD population. It is also important to state, by whom these studies were done – there are no references.

Response:
The first sentence has been corrected to reflect that although there are studies available, there are fewer focused trials in this population. This is meant to be a general statement with specific references provided throughout the manuscript as each drug is outlined.

4. Aspirin: "irreversibly blocks Thromboxane A2 in the platelet". Thromboxane production is secondary, due to irreversible inactivation of cyclooxygenase enzyme.

Response:
Mechanism of aspirin has been corrected.

5. Clopidogrel, p.8: The paragraph on CHARISMA study compares aspirin vs clopidogrel-aspirin, and must be therefore discussed in the subchapter dedicated to dual vs mono therapies together with MIRROR study.

Response:
This paragraph has been moved to the dual vs. mono section as recommended.

6. Clopidogrel, p.8: "Patients with multiple risk factors for PAD are also more likely to express clopidogrel resistance including diabetes [21], smoking [22], and chronic kidney disease (CKD). [23]" This sentence does not make sense, please rewrite.

Response:
This sentence has been rewritten for clarity.

7. Ticagrelor: "Ticagrelor (….) like prasugrel, has a greater platelet inhibition than clopidogrel". It may cause, but not "have" greater inhibition. Please correct.

Response:
Corrected.

8. Dual vs Mono Therapy: What was the size of the study population in MIRROR trial?

Response:
Eighty patients, added to the manuscript.

9. Role of anticoagulant therapy: In the previous chapter, dedicated to anti-platelet agents, the mechanism of action is briefly highlighted for each drug. The same must be done in this chapter, for warfarin, or DOACs.

Response:
Mechanisms of action for oral anticoagulants have been added.

10. Warfarin: "The WAVE trial compared the efficacy and safety of combination antithrombotic therapy with an antiplatelet agent and an oral anticoagulant to antiplatelet therapy alone in patients with PAD. Results showed that combination therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications." The authors forgot to mention which antiplatelet agent and which oral anticoagulant (presumably warfarin) have been used in the trial. Please provide missing info!

Response:
This was an oversight on our part and has been corrected.

11. Antiplatelet therapy and patency post peripheral endovascular treatment: In this sub-chapter, the PTA results are totally mixed with studies concerning grafting. The two procedures, and the respective data on anti-platelet therapies in these procedures, should be discussed separately!

Response:
We have made the corrections and discussed the two procedures separately.

12. P.15. CASPAR trial: it is unclear why CASPAR is in brackets. Furthermore, in this paragraph the authors suddenly abbreviate "aspirin" as "ASA". Please correct.

Response:
Corrections made.

13. Current Practice: The sentence ”Rationale for shorter duration of antiplatelet therapy is primarily drawn from the fact that stenting is reserved for flow limiting localized complications and endothelial damage mainly from balloon angioplasty” is not clear, as especially patients with DES require

Response:
We are unable to comment fully on this comment, since the recommendation is cut off. We have done our best to address this issue however.

We have rephrased the sentence. We want to imply that since stenting in patients with lower extremity PAD is mostly reserved as last resort in case we get sub-optimal results after PTA or flow limiting complications, hence it is speculated that patients might not need prolonged duration of antiplatelet therapy after just balloon angioplasty unlike percutaneous coronary interventions where stents are invincible.

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Dear Dr. Fang-Fang and Dr. Lian-Sheng Ma,

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Title: Peripheral Interventions and Antiplatelet Therapy: Where Do We Stand in an Era of Guideline Based Therapy?

We would like to thank you and your reviewers for the second thorough review of our manuscript, and for liking it with a high potential for acceptance following the final mini-reviews.
ALL reviewers' comments/concerns/suggestions were addressed on a point-by-point basis, and changes were made in the manuscript text accordingly.

The title was also modified, according to your suggestions/guidelines to:
"Peripheral Interventions and Antiplatelet Therapy: Role in Current Practice."

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.
Conflict-of-interest statement: None of the authors has any of interest.

We hope you find the manuscript acceptable for publication in its current format.
Should you need anything else, please do not hesitate to contact me.

Sincerely,

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