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Professor Jia-Ping Yan
Science Editor
World Journal of Cardiology

RE: 51088

Dear Dr. Yan,

We are pleased to submit our revised manuscript, "CO₂-angiography for patients with peripheral arterial disease at risk of contrast-induced nephropathy" for consideration for publication in *World Journal of Cardiology*.

We describe the associated risks, pathophysiology, incidence, and economic burden of contrast induced nephropathy (CIN), while highlighting current technological advances in the delivery of CO₂ in vascular angiography for patients with peripheral arterial disease (PAD) and critical limb ischemia (CLI). Hybrid angiography, using combined CO₂ and reduced amounts of iodine, has been demonstrated to reduce the incidence of CIN, making angiography a safe procedure for this patient population. Additionally, methods to overcome challenges and contraindications of CO₂ angiography were carefully detailed to enhance clinical practices. Lastly, we also provide real-world findings from the office-based laboratory service of our vascular lab that illustrate the clinical impact following the use of hybrid CO₂ angiography in the management of patients with PAD and CLI who are at risk of CIN.

We thank the reviewers for their insightful review of our manuscript and for their constructive suggestions. Based on the comments from the reviewers, we have made the requested changes to the manuscript in bold text. There is also the addition of an author Dr. Akinsansoye Dosekun who has helped critically review this manuscript. He has signed the Copyright Agreement which has been re-uploaded as well. We have also addressed the comments from the reviewer and believe these revisions have strengthened the manuscript. The reviewer's comments are listed in bold font below, followed by our responses in italic font. We believe this review complements the work published in *World Journal of Cardiology*. We confirm that this work is original and has not been published elsewhere, nor under consideration for publication elsewhere. Please address all correspondence concerning this manuscript to me at amol@vipplc.com. Thank you for your consideration of this manuscript.

Sincerely,

Amol Gupta

Comments to the Author

1. As far as I am concerned, the key words shown in this review, including peripheral artery disease (PAD), angiography, vascular medicine, chronic kidney disease and hypertension, somewhat lack of accuracy. For example, I didn't found any demonstrate about "hypertension" in this review.

We thank the reviewer for this thoughtful suggestion. A new, more accurate set of key words have been added to the manuscript.

2. This review lacks the analysis in the pathogenesis of CIN. It demonstrated the protective effect of hybrid angiography in patients with PAD at risk of CIN is associated with the reduction of iodine volumes. I wonder whether other pathogenesis of CIN also plays an important role in the prevention of CO₂-angiography in patients with PAD at risk of CIN, such as oxidative stress, inflammation, and vasoconstriction. Moreover, this review lacks the report about the association of iodine volumes and the incidence as well as the severity of CIN in patients with PAD, which would help directly illustrate the protect pathogenesis of CO₂-angiography in patients with PAD at risk of CIN.

We agree with the reviewer that the pathogenesis of CIN is an important topic to review and adds value to the manuscript. A section illustrating the different pathogenic contributing factors has been added. We have also added a brief discussion regarding the association of contrast volumes and CIN incidence.

3. Although the complications associated with the use of CO₂ are uncommon and are usually minor and transient, I think it would be better if you can demonstrated the associated preventive and therapeutic strategies for the complications and list a table similar to "contraindications of CO₂-angiography"

We thank the reviews for this suggestion. A table (Table 2) outlining the two major CO₂-associated complications and their preventative/therapeutic strategies has been added to the manuscript.

4. This review unable to provide a comprehensive review about the limitation and advantages of currently preventive and therapeutic strategies including hydration, avoid the use of nephrotoxic medication, antioxidant for CIN, I think the comparison between CO₂-angiography and this existing preventive strategies in ameliorating the incidence and severity of CIN deserves further discuss.

We agree with the reviewer that a comprehensive review of the limitations and advantages of the current strategies to prevent CIN would be beneficial. We have included statements further describing the beneficial effects and limitations/contraindications of these methods. Currently, there have been no direct studies comparing CO₂ angiography and the existing preventive strategies for contrast mediated angiography; therefore, no direct comparisons were extrapolated for this manuscript.