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Response to Reviewers-Manuscript # 14279

Name of journal: *World Journal of Hypertension*

Reviewer #1

Reviewer: This is an interesting paper which may improve our knowledge in the fiels. The subject matter is suitable for the intended audience and it fits the journal scope. Article is mostly clearly written, but Title is suggestive of the article's content. Article is appropriately organized and the headings are indicative of content I suggest to accept this paper in the present form.

Response:

Thank you for your favorable comments.

Reviewer #2

Reviewer: … several confounding factors that include variations in the denervation procedure, changes in patient medications, and differences in drug adherence may have impacted trial results. Therefore, all these confounding factors should be considered in the design of future renal denervation. The subgroup analysis might be necessary to explain the results of renal denervation. These confounding factors should be mentioned in this review. Furthermore, at least two articles published in Hypertension after Symplicity-3 might be helpful to revise this article.

Response: Thank you for the suggestion to include other factors which could have impacted the results of the Symplicity-3 trial and the need to update this rapidly changing field of renal artery denervation. Accordingly, we have inserted additional published critiques of the Simplicity-3 trial which indicated a number of responses, i.e., letters to the editor, all of which suggested various explanations for the failure of the simplicity-3 trial. In addition we have also referred to a recent released consensus document from the Joint UK Societies (2014) by respected investigators in the field indicating potential flaws in the Symplicity-3 trial. These revision in the text have been underlined (see pages 4, 5).

Reviewer #3

Reviewer: Authors' hypothesis is unconvincing since a sham group is the best way to show if a procedure is effective. Simplicity-3 is a methodologically sound trial with immaculate data. Authors should focus their criticism on procedure deployed in the

clinical practice well before the demonstration of their efficacy and without passing the health technology assessment.

Response: To address the reviewer's statement, "Simplicity-3 is a methodologically sound trial with immaculate (*without fault or error*, italics ours) data" we have inserted additional published critiques of the Simplicity-3 trial which indicated a number of responses, i.e., letters to the editor, (reference) all of which suggested various explanations for the failure of the Simplicity-3 trial, ranging from operator inexperience, to questions of medication compliance to inclusion of obese or black patients, among others. It is interesting to note that Dr Bhatt, the lead investigator in the Symplicity-3 who stated, "We agree that various selection criteria and characteristics of our patient population-such as the exclusion of patients with white-coat hypertension, the inclusion of obese patients and a variety of baseline characteristics or medications could account for the null results of this trial, as compared with the findings of previous trials." Thus, the lead investigator concedes that trial differences could have been the basis of the negative results for Symplicity-3. We suggest that the focus of each of the Simplicity trials on ablating the variable structure of the post-ganglionic axons on the renal artery adventitia provides and important impediment for achieving sympathetic denervation. Indeed, the percent of non-responders in a number of previously reported studies ranges from these studies ranges from 10-43 % (Schlaich et al. Curr Hypertens Rep 2012;14: 247-253; Persu et al. J of Human Hypertension 2014;28-150-156