Reviewer’s report

Title: Heart Rate Variability and Target Organ Damage in Hypertensive Patients

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Reviewer: Ruan Kruger

Reviewer’s report:

The authors of this manuscript "Heart Rate Variability and Target Organ Damage in Hypertensive Patients" aimed to evaluate the link between HRV and measures of TOD in hypertensive patients. Please consider the following revisions:

Major Compulsory Revisions

1. The authors state that a sample population was selected from 12 000 patients. However, no indications of excluded number of patients (n-values) were given. Indicate the number of patients respective to their disease state or exclusion criteria.

2. In the method section under the sub-heading Echocardiography the authors were not specific in which window the M-mode measurements were performed. Was it perhaps the standard PLAX window or the preferred PSAX window? Was it parasternal or apical views?

3. The reference for LV parameters is very old and out-dated. There are more recent guidelines of the ASE (2005). I would suggest that the authors revise their reference list.

4. The citation of Devereux and Reichek is a 1977 paper. However, Devereux had updated publications in 1986 and 1987. Furthermore, I question the validity of the LV mass index calculation by Devereux et al. The ASE cubed formula is the standard and preferred method to quantify the mass of the left ventricular tissue. Could the authors reason or defend this shortcoming?

5. The authors mentioned that all measurements were analyses by three different trained experienced physicians. What is the inter-variability between those three physicians concerning the location and analysed section of each carotid artery? Are their methods calibrated?

6. The IMT measurements were analysed offline. Could the authors perhaps provide the software and version that was used to process these images at the offline workstation?

7. The PASW version 18 software is now the licenced property of IBM SPSS. I suppose the authors need to revise their reference to this software before publication.

8. I have major concerns regarding the result tables. In Table 1: Have the authors
considered testing for interaction on the main effect of gender within this selected sample of patients? If so, please provide the statistical information to support the reason why the groups were not divided into men and women, separately. In Table 2: There is no information to guide the reader on the type of value that is reported in the table. Are these n-values per category or percentage out of the total sample? Table 3: The authors referred to Table 6 in the result section when they meant Table 3. Tables 3, 4 and 5: The one probability value reported in each table, does it refer to the trend observed within each independent variable (in other words: Are these tertile subdivisions)? The data presented in Tables 4, 5 and 6 are not clearly described and the tables could be supported by a footnote to clear the uncertainty.

9. In the final sentence of the second last paragraph of the result section the authors wrote: "Higher value of systolic blood seems to be associated..." What do they mean by systolic blood? Is it the pressure? Rather consider the following: "Elevated systolic blood pressure seems to be associated..."

10. In the final paragraph of the result section the authors refer to vascular involvement and later on vascular conditions. What is meant by these statements? Should it perhaps be vascular changes or alterations?

11. The authors state in the first paragraph of the Discussion that this was the first study to investigate HRV measures in hypertensive patients by TOD levels. However, later on in the Discussion they refer to Garcia-Garcia who did exactly that. I struggle to find the uniqueness of this study compared to Garcia-Garcia apart from the age and metabolic adjusted model.

12. On the same issue the authors state that they have considered metabolic factors to control for such as glucose and cholesterol. My question is: What about body mass index or waist circumference or body surface area? Surely if echocardiographic data was recorded one should have anthropometric data?

Minor Essential Revisions

1. In the abstract under the result section of the second sentence the authors refer to plague in respect to IMT. The use of the word plague is incorrect and should be spelt as plaque. This error is also in the following sections of the manuscript: (i) the third paragraph of the result section of the main manuscript after table 3 in both the first and second sentence; (ii) also in the seventh paragraph of the result section, the second sentence; (iii) the second paragraph of the discussion in the third sentence, and; (iv) finally in the conclusion paragraph in the second sentence line 3.

2. The authors use the following phrase on numerous occasions: "... and particularly, kidney one..." This makes no sense to the reader. The authors must revise this sentence in all sections (see below) to the following: "... and particularly the kidney, ..."

These errors are found in the abstract under the: (i) conclusion section in the
second sentence; (ii) the fifth paragraph of the discussion in the second sentence, and; (iii) in the conclusion section sentence number four.

3. In the first paragraph of the Background the authors repeated the words "significantly related" twice back-to-back. This is in the second sentence.

4. In the second paragraph of the Background in the first sentence, the authors mentioned at the end "..., including CV [7]." Are they referring to CV events, CV disease, CV changes or what?

5. In the first sentence of the third paragraph of the Background the authors overused the word "of". The sentence should read: "... by therapeutic correction of any modifiable risk factors, ..."

6. Also in the same sentence at the end it should read: "...diabetes, smoking habit or physical inactivity."

7. The final sentence of the final paragraph in the Background section makes no sense. Were the patients provided with the centralized database? Perhaps it should be: "... and community hospitals networked with the centre, and providing a centralized database including demographics and clinical information of the patients."

8. The authors must conform to a standard language format i.e. either American or European. There are inconsistencies regarding the spelling of numerous words in different language spelling rules. E.g. the use of "s" instead of "z" OR the use of "-er" instead of "-re".

9. The final sentence in the Ethics section of the Methods is written in passive voice. This is confusing, so please check the grammar.

10. Under the sub-heading Statistical analyses the authors abbreviated the Chi-square test as "c test"; it should be c2 test.

11. The authors should mention the confidence intervals as ±95% confidence interval and not only 95% confidence interval.

12. The authors overused the word "by" in the last sentence of the first paragraph of the result section and it should read: "... categorized by eGFR, IMT and LVH."

13. In the result section in paragraphs 4 and 7 the authors wrote VLH instead of LVH!

14. The authors are inconsistent with their use of capital letters throughout the result section where they use the word "group" sometimes with a capital G or sometimes with a small g.

15. In the second last paragraph of the Discussion the third sentence begins oddly. I'd suggest that the authors start like this: "Our results were consistent..."

16. Also in the second last sentence of the second last paragraph of the Discussion the authors' grammar is incorrect. The sentence should read: "...,
could be selected either in short-term recordings under standardized conditions[42] or in long-term...

17. In the final paragraph of the Discussion the authors should rather write "systolic blood pressure values" than "values of systolic blood pressure"

18. In the final paragraph of the Discussion the sentence should read: "...controlled in patients with moderate renal eGFR by the (significantly higher) use of ..."

19. The final sentence of the Conclusion is too long. Consider revising: "...particularly the kidney are not clearly known. We suggested that further..." AND at the end of that same sentence "...early stages of hypertension and prior development..." (not prior to...)

Discretionary Revisions

1. The final sentence in the second paragraph of the Background section is too long. Split it in two, by doing the following: "..., and white coat hypertension[18]. Moreover, decreased..."

2. In the fourth paragraph of the Background in the first sentence the authors referred to the recent paper by Garcia-Garcia. However, the sentence reads difficultly. The authors should add the word "a" or "the" before the words "...recent paper..."

3. There are too many of these words to pinpoint in this feedback. However, the authors must read through this manuscript to ensure that all plurals and article grammar is correct. There are many words such as profile_, odd_, diuretic_, patient_, value_, drug_, etc. that have an "s" missing at the end of each of these words. Also the authors must use the article grammar in front of words such as a recent paper (also mentioned earlier), a one-month antihypertensive therapy wash-out, a 24-hour ECG, an adjusted model, on the heart, etc.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.