September 24, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (fine name: 4632-review.doc).

Title: Blood Pressure Variability and Cerebrovascular Disease

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Name of Journal: *World Journal of Hypertension*

ESPS Manuscript NO: 4632

The manuscript has been improved according to the suggestions of the reviewers:

1. Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewed by 00396771

This brief review addressing the impact of blood pressure variability in cerebrovascular diseases is based mostly on few hand-picked clinical studies. While a good overview of the issues is given, the authors might want to expand on the meaning of blood pressure variability by giving the reader more details on what is actually being measured (e.g. time domain vs. frequency domain, sympathetic modulation vs. parasympathetic modulation ...). Also, more details regarding the correlation between drugs capable of reducing BP variability and also improving the stroke condition is needed. Finally, the authors should include some general literature within the introduction to help the reader get familiarized with the background issues.

- The purpose of this manuscript is to present a general overview of BP variability, --a poorly evaluated aspect of BP--, rather than an in-depth comprehension review of this topic. The heterogeneity of BP variability measurements in the different studies makes it difficult to establish which is the most appropriate. Probably, when ABPM or home blood pressure is assessed is not the same than analysis of BP variability in the long-term. Future studies probably will shed some light on this regard.
- This aspect is commented on in the first paragraph of DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS with references #14 and #30 for more extensive information. In the same section, the contributions of Rothwell and associates (references #31 to #33) in the retrospective analysis of results of the ASCOT-BPLA

trial and other cohorts of patients with history of TIA, also mentioned on page 6 (reference #14), regarding the differences of different antihypertensive drug classes on BP variability and the stroke risk.

- In the INTRODUCTION, we have added two new references (#1 and #2) supporting the following sentences " … it was shown that this short-term BP variability was an independent risk factor of cardiovascular morbidity and mortality" (reference #1, Mancia G, et al. Hypertension 2007;49:1265-1270) and "On the other hand, BP variability involves different concepts, which in turn adds difficulty in the definition and assessment of its relevance from a clinical perspective" (reference #2, a review of Mancia G et al. Hypertension 2011;57:141-143).

(2) Reviewed by 00506263

Author has discussed about ABPM for measuring blood pressure as surged hypertension and night-time blood pressure increasing it should be discussed about home blood pressure measuring, too. Page 9, line 12; posthoc must be post hoc.

- The contribution of home blood pressure in the analysis of BP variability as risk factor is discussed in ***Medium- and long-term variability*** section, with supporting references #11 and #12.
- The spelling error is corrected.

(3) Reviewed by 00608229

This is a meticulously conducted review that critically summarizes most of the information available in the literature on this important topic. Minor concerns and suggestions are provided below.

1. Information provided in Introduction section needs to be documented with relevant references.

- This comment was also made by another reviewer. In the INTRODUCTION, we have added two new references (#1 and #2) supporting the following sentences " … it was shown that this short-term BP variability was an independent risk factor of cardiovascular morbidity and mortality" (reference #1, Mancia G, et al. Hypertension 2007;49:1265-1270) and "On the other hand, BP variability involves different concepts, which in turn adds difficulty in the definition and assessment of its relevance from a clinical perspective" (reference #2, a review of Mancia G et al. Hypertension 2011;57:141-143).

2. *Page 4 – Paragraph 2: The notion expressed by the authors "…that these alterations may be related with sleep-disordered breathing, particularly obstructive sleep apnea…" should be supported with citations.*

- We have added two new references to support this statement. References #8 and #9 (Kario K. Obstructive sleep apnea syndrome and hypertension: ambulatory blood pressure. Hypertens Res 2009; 32:428-32; and Johansson JK, Kronholm E, Jula AM. Variability in home-messured blood pressure and heart rate: associations with self-reported insomnia and sleep duration. J Hypertens 2011; 29:1897-1905).

3. Page 4 – Paragraph 2: The authors should clarify whether the crucial factor of the association between short-term BP variability and CV events is the excessive nocturnal dipping of BP (as it appears to be in most cases) or the nocturnal rise of BP due to obstructive sleep apnea.

- We have added this sentence: "The excessive nocturnal dipping of BP and a nocturnal rise of BP due to obstructive sleep apnea have been both considered important factors of the association between short-term BP variability and cardiovascular events but, in our opinion, it cannot be currently established which of the two factors is related to a higher cardiovascular risk."

4. Page 4 – Paragraph 3: The limitations of the very interesting meta-analysis of 11 different populations by Hansen et al. should be discussed.

- This new sentences are added: "The authors of this interesting meta-analysis, however, recognized the limitations of the study, which referred to the general applicability of results (particularly to Africans of black ancestry and African Americans), the fact that intermittent techniques of ABPM are less precise to capture short-term BP variability than continuous BP recording, and the low power to detect variability among strata (e.g. considering a tw-sided α-level of 0.05, the power to detect a 0.24 difference between normotensive and hypertensive subjects in the log-transformed hazard ratio of all cardiovascular events was only 46%)".

5. Page 5 – Paragraph 2: Since the authors provide home BP variability measurements from the Ohasama cohort, a comparison of such data with ABP monitoring in terms of correlation and/or level of agreement would be of interest.

- The content of this report regarding BP variability measurements from the Ohasama cohort does not include data to assess the correlation and/or level of agreement with ABPM.

6. Page 5 – Paragraph 3: A visual aid for the readers might be a figure from the INVEST study illustrating that "…as proportion of visits with BP control increased there was an associated steep reduction in the cases of stroke".

- We have added a figure (Figure 1) showing the decrease in hazard ratio (95% confidence interval) for fatal and non-fatal stroke as the percentage of visits with BP control increases from < 25% (reference) to ≥ 75% in the INVEST study.

7. Page 6 – Paragraph 1: The authors could elaborate more on the finding that "…this relationship between BP variability and risk was also demonstrated in a population with strictly normal BP."

- We have rewritten the sentence as: "This relationship between BP variability and risk of mortality for all causes was also demonstrated in the subset of the study population with strictly normal BP[15]".

8. Page 7 – Paragraph 2: Long-term visit-to-visit SBP variability was independently associated with a higher risk of subsequent mortality and MI but not stroke in the recently published Cardiovascular Health Study, a longitudinal cohort study of vascular risk factors and disease in 3852 elderly subjects (Am J Hypertens. 2013 Jun 6. [Epub ahead of print] Suchy-Dicey AM et al. Blood Pressure Variability and the Risk of All-Cause Mortality, Incident Myocardial Infarction, and Incident Stroke in the Cardiovascular Health Study). The above information could be added in the Medium- and long-term variability section after the data from PROSPER.

- This information and the reference to this study are included. The new sentence reads: "These results are consistent with recently published data of the Cardiovascular Health Study, a longitudinal cohort study of vascular risk factors and disease in 3852 elderly subjects in whom long-term visit-to-visit systolic BP variability was independently associated with a higher risk of subsequent mortality and myocardial infarction but not stroke[19]."

9. Page 7 – Paragraph 2: Could the authors possibly speculate on why visit-to-visit variability of BP was an independent predictor of all-cause and vascular-related mortality, but not of stroke, in the elderly in the PROSPER study, although such associations strengthen with advanced age?

- We have added this comment: "Since the reliability of BP variability increases with the number of measurements, authors of the PROSPER study suggested the possibility that measures of BP variability every 3 months during the randomized phase of the trial (mean follow-up 3.2 years) may still have underestimated the true effect of variability on clinical outcomes[18]."

10. Reference 14 should be corrected to PLoS ONE 2012; 7: e52438 11. The text should be edited by a native speaker.

- Corrected.

3 References and typesetting were corrected

Please note, that the new text is highlighted with the pen function of Word.

Thank you again for publishing or manuscript in the *World Journal of Hypertension.*

Sincerely yours,

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