Author's response to reviews

Title: Association between different measurements of blood pressure variability by ambulatory blood pressure monitoring (ABPM) and ankle-brachial index

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July 16, 2010

Melissa Norton, MD
Editor-in-chief
BMC Cardiovascular Disorders

MS: 1243547668354845 - Association between different measurements of blood pressure variability by ambulatory blood pressure monitoring (ABPM) and ankle-brachial index

Dear Dr. Norton,

Enclosed is a second revised version of our manuscript. At first we were disappointed with the new requests from one reviewer, it is always difficult to deal with new and new comments. But afterwards we considered some of them insightful to extend the interpretation of our findings, and comments addressing such findings were included in the new version. Thanks again for the editorial processing of our contribution, we hope to be at a very close ending of our submission.

Sincerely yours,

Flávio Danni Fuchs, M.D., Ph.D.
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Reviewer’s report

Major compulsory revisions:

1. The statement regarding exclusion of 3 subjects from linear regression should be moved to the statistical methods section.

Response: done.

2. Rather than separate linear regressions of the left and right legs, I would suggest either a model of the lower ABI (one measure per subject) consistent with the logistic regression models or a mixed model that includes both measures and accounts for the within-subject correlations. Separate models would be appropriate if side of the body were a major modifier of the association between the BP variability measure and ABI, but this does not appear to be the case. In any individual, either side may have a greater degree of atherosclerosis and it would seem more appropriate to model taking this into account.

Response: we followed the suggestion and ran a model entering the worst leg of each individual and all statistics went away, even those from other variables, see below the output. I am not a statistician but I think that my fairly experience from the last 30 years allows to interpret the findings: the multiple linear model requires a full range of values of variables to capture the association between them; with the limitation to the worst leg such amplitude was artificially reduced, reducing the power to detect linear associations between dependent and explanatory variables. Therefore we decided to leave table 3 as in the original.

Model Unstandardized Coefficients Standardized Coefficients t Sig.

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
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<tr>
<td>1 (Constant)</td>
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<td>1.271</td>
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<tr>
<td>timerate</td>
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<td>2.963</td>
<td>.043</td>
<td>.792</td>
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<tr>
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<td>.028</td>
<td>-.001</td>
<td>.981</td>
</tr>
<tr>
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<td>.022</td>
<td>-.052</td>
<td>.966</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Diabetes</td>
<td>-.047</td>
<td>.945</td>
<td>.345</td>
<td></td>
</tr>
</tbody>
</table>
3. The analysis including the pulse pressure is fine, and the sentence added to the results sufficient.

Response: OK.

4. Although only 3 subjects had high ABI, I would suggest excluding them from the logistic regression models and re-running. It is not universally agreed that these values represent ‘abnormal’ ABI in the same sense as a low ABI, and the inclusion of these values may introduce noise into the analysis. Depending on the results, a statement that the exclusion of these subjects did not substantially change the results could be included or the results of the models excluding the subjects could be presented.

Response: We ran the models excluding these individuals. The new estimates were the following, showing that the direction did not change but became a little bit more strong (with wider CIs). We added the following result in the text:

With the exclusion of three individuals with abnormal ABI because of higher values, the risk ratios increased and were almost significant in the full model: RR 18.7 (95% CI: 1.96-198.5; P=0.01) when adjusted for age and RR 10.7 (95% CI: 0.89-129.1; P=0.06) when adjusted for age, diabetes and 24-hour systolic blood pressure.

5. The linearity of the association of continuous predictors with ABI in the models should be checked. This could be done one-at-a-time, for example, by including polynomial terms (quadratic and cubic) and testing for their significance. A linear model with >400 subjects should accommodate 40 predictors and a logistic regression model with almost 60 ‘events’ should accommodate 6 predictors, therefore, the inclusion of 3 terms in a model, testing for the simultaneous significance of 2 of these, should not pose any major difficulty.

Response: We did this, and both the quadratic (P = 0.169) and the cubic (P = 0.157) did not have stronger association with the outcome, excluding a relevant non-linear relationship. Please, note that the risks and CI of table 2 part 2 are slightly different from the original, when we ran the model we identified a mistake in the translation of findings. We added the following statement in results:

Models with the quadratic and cubic term of the time-rate did not improve the intensity of association, therefore excluding a relevant non-linear association.

Minor essential revisions: None

Discretionary revisions:

1. Regarding the additional utility of BP variability above the BP itself, the c index – which represents the area under the ROC curve – is readily computed from logistic regression. (This is provided as part of standard output for logistic regression in SAS, and may be available in SPSS.) The c indexes from the
models including BP with and without the time-rate index could be presented. Although these models are not prognostic of cardiovascular outcome directly, and the addition to the Discussion is good, the ABI is being evaluated as a sort of surrogate for outcome in this study and more information could be provided.

Response: we ran the models with systolic and diastolic blood pressure and afterward adding the time-rate index (see below). It did not increase substantially the c-index.

Systolic plus diastolic: .637 (.559 to .714)

Systolic plus diastolic plus time-rate: .648 (.575 to .722)

We added the following phrase in results: Adding the time-rate index to a model with systolic and diastolic blood pressure the C-index increased from 0.637 (95% CI 0.559 to 0.714) to 0.648 (95% CI 0.575 to 0.722).

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report