Reviewer’s report

Title: Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study

Version: 0 Date: 04 Dec 2018

Reviewer: Marguerite Irvin

Reviewer's report:

Comments to Author:

The authors have presented a pertinent hypothesis - "Resistant hypertension as an independent predictor for all-cause mortality in individuals with type 2 diabetes: a prospective cohort study" in this large sample size data using the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter study. The authors have built on their prior work, and conclude that resistant hypertension did not predict death beyond target organ damage in high risk population of type 2 diabetes. The strength of the paper is the longitudinal format up with minimal loss to follow up, detailed information on hypertensive treatment, and appropriate statistical approach. By defining hypertension phenotypes in detail, the authors have attempted to assess the association to a granular level. However, comparison within groups have increased the complexity of overall analysis. Below are few concerns for author's consideration:

Major Comments:

1. The hypertension status of the participants is determined at the baseline and these individuals are subsequently followed for around 10 years. Considering this population is quite old, there are always a possibility that individuals from lower hypertension category are more likely to evolve into higher hypertension category (untreated hypertension → treated hypertension, or controlled hypertension → resistant hypertension) over this long follow-up period. So the significant association of all the hypertension phenotypes with mortality or J-Shaped phenomenon observed here could potentially be attributed to more severe hypertension developed over time in these individuals. This introduces a misclassification bias which is a major concern in the interpretation of these analyses. The authors should address the limitation in the discussion, including lack of availability of multiple time points over time.

2. There is a discrepancy in the figures and tables and stated conclusions. While the figures and tables focused on comparison of hypertension phenotypes with normotensive group as reference, the authors preferentially highlighted the comparison of controlled hypertension vs uncontrolled hypertension as the concluding finding. With insufficient information on pair-wise comparison, there are concerns to affirm with their concluding
findings. The authors should also further clarify the phrase "beyond target organ damage".

3. The authors have not provided detailed information on ascertainment of mortality data.

4. The authors should consider including heart failure in the model if available. It would be interested to see if controlled hypertensives still have increased mortality risk in comparison to other groups after adjustment. From the descriptive table it seems there is a higher burden of CVD in that group. Prior studies have observed that the heart failure is an important factor associated with mortality in diabetic population.

5. Model 2 includes diabetes duration, HbA1C and anti-hyperglycemic treatment which are likely to be highly correlated. The authors should determine if only one or two terms are needed.

6. Did the authors correct for multiple comparisons in the survival analysis? The authors mentioned Bonferroni correction, however did they limit the correction to ANOVA for post-hoc comparison? They have not presented these findings in the result section.

7. The conclusion seems radical that less stringent BP goals are needed in high risk T2D patients. It seems these results need to be further vetted and validated in at least one independent population.

Minor Comments:

Methods:

1. The study population mentions that patients are attending tertiary care hospital from 19 areas. Does the mortality rates here also include in-hospital deaths? The mortality rates can be affected by quality of care offered by hospital, and may vary by that. Did the authors consider accounting for variability in the hospital?

2. The authors mention "in separate analyses, models were further adjusted for either BP or pulse pressure values at baseline". Are these values different from BP parameters used to define hypertension groups? The rationale behind understanding the association between BP values, in addition to hypertension categories, with mortality is not clear.

3. Did authors adjust for anti-platelet and anti-coagulant treatment?
Results:

1. Median follow-up time is more informative in time to event analysis than mean follow-up time. It will be helpful if that is provided.

2. Can authors provide number of deaths within each group in Table 1?

3. Table 2. For anti-hypertensive groups, were normotensive or untreated hypertension included as categories in X2 test?

4. Page 11 -line 55 to page 12 -line 2. Did authors compare resistant hypertension with other hypertension categories? The authors mentioned comparison between resistant hypertension and controlled hypertension only.

5. Abstract - results Line 1 - the reference group here is non-hypertensive group. Based on the results, it may not be appropriate to say that resistant hypertension group has higher hazard ratios compared to all other groups unless the authors compare each group with resistant hypertension. The authors should provide these results or alternatively modify the sentence.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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