Author’s response to reviews

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

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Author’s response to reviews:

Reviewer #2

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:

We thank the Reviewer for her positive overall judgement of our work and for providing us with useful suggestions to improve the manuscript.

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.

We thank the Reviewer for raising this important issue. Previous studies on resistant hypertension (RHT) and mortality have classified patients based on blood pressure (BP) values measured either at baseline (please, see refs # 13 and 15), as in our study, or over the first 1-2 years of follow-up (please, see refs # 8, 12, and 18) and have followed them for a number of years thereafter to collect information on vital status. As suggested by the Reviewer, this introduces a potential misclassification bias as some of the participants could have changed BP status category during the follow-up period. As discussed in our manuscript, this has presumably occurred for individuals with untreated hypertension (UTHT, i.e., receiving no anti-hypertensive agent) or uncontrolled hypertension (UCHT, i.e., not on-target with 1-2 drugs), as it is likely that they subsequently received a treatment or a more aggressive one, thus experiencing a reduction of BP levels, with some of them falling into the resistant hypertensive category” (please, see page 14, line 27). This is the reason why we separated these individuals from those with controlled hypertension (CHT, i.e., on target with <3drugs) instead of pooling them in the category of non-resistant hypertension, as done in the studies mentioned above. However, we agree with the Reviewer that, during the 10-year follow-up, some NT individuals may have become hypertensive and also participants with CHT or RHT and those falling in the controlled (CRHT) or uncontrolled (UCRHT) RHT categories may have changed their BP status category,
though not necessarily they have evolved into a higher category, as it is possible that CHT individuals have become RHT but also vice versa, as shown in a retrospective analysis of a group of US Veterans with RHT (please, see ref # 34). Thus, we agree that this represents a potential bias of our study and we have now acknowledged it among the limitations (please, see page 15, line 6).

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".

We agree with the Reviewer that there is a discrepancy between figures and tables (focused on comparison of hypertension phenotypes with normotensive group as reference) and the text in the Results and Discussion (which highlight the comparison between CHT and RHT and then between CHT and CRHT). The reason for doing this was that we wanted to:

a. estimate the risk of death associated with each hypertension phenotype compared with the normotensive group to assess whether and how much this risk is increased, as expressed by hazard ratios (HRs) and lower 95% confidence values higher than 1;

b. compare the mortality risks associated with CHT and RHT (or CRHT) to assess whether RHT predicts death independently of the hypertension status per se as well as of cardiovascular risk factors and target organ damage, as previously shown in the general hypertensive population (please, see refs # 13-15 and 18) and also in hypertensive individuals with cardiovascular disease (CVD) (please, see refs # 19-21) or chronic kidney disease (CKD) (please, see refs # 22 and 23).

However, as the latter was the primary objective of our study, we have now compared all the other hypertensive phenotypes and the normotensive group with the RHT (or CRHT) category as reference. Thus, from the same analysis we have obtained both (a) the comparison between RHT (or CRHT) and the normotensive group (and also UTHT, UCHT, and UCRHT participants), as an ancillary observation; and (b) the comparison between RHT (or CRHT) and CHT, as the primary finding of the study. The results of these new analyses have confirmed those previously obtained in the separate analyses of RHT (or CRHT) versus the normotensive group (and the other groups) and RHT (or CRHT) versus CHT, though they did not provide information on the comparison between the other hypertensive phenotypes and the normotensive group, which however is beyond the scope of our work. This should address all the Reviewer’s concerns about the complexity of the analysis and make the study results easier to understand by the journal’s readers.
The reason why we did not use this strategy in the original version of the manuscript was that, in this way, significant differences between RHT (or CRHT) participants and the other groups are expressed by HRs and upper 95% confidence values lower than 1 indicating a significantly lower risk associated with the other groups compared with RHT (or CRHT) instead of a significantly higher risk associated with RHT (or CRHT) compared with the other groups.

The phrase "beyond target organ damage" refers to the data from Model 3, which adjusted for target organ damage complicating both type 2 diabetes and hypertension, i.e., the long-term complication of diabetes CVD, CKD, and retinopathy, which are more frequent in RHT than in non-RHT individuals, as reported in previous studies, including a prior publication from the RIACE cohort. As requested, this has been further clarified in the revised version (please, see page 13, line 8).

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

As stated in the Methods section (please, see page 16, line 6), the Italian Health Card database is a national system that provides updated and reliable information on vital status of all current Italian residents. This database is used by both the Ministry of Finance and the Ministry of Health of Italy for tax and health care purposes, respectively. Therefore, it include all current Italian residents, temporary or permanent, as all of them are required to make the tax return and have right to health care. This is the reason why their vital status must be taken updated by centrally collecting and recording all death certificates within 24-48 hours.

In any case, as health care is provided directly by the 20 Italian regions, all mortality data obtained from the Italian Health Card database, including dates of death, were verified by interrogating the regional health care databases. This double-check revealed no discrepancy between the national and the regional databases, further supporting the validity of the method used for retrieving information on vital status.

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.

As widely recognized, the definition of heart failure as a study endpoint is difficult. Indeed, hospitalization for heart failure, the most used definition for this endpoint, may be adequate to capture only more severe heart failure and, hence, it is useful as evidence of exacerbation of the underlying disease in observational studies or intervention trials of heart failure. Conversely, in
low risk cohorts, as in observational studies in the general population or in intervention trials for primary prevention, objective criteria of myocardial dysfunction are probably necessary to confirm a new heart failure diagnosis (please, see refs Zannad et al. Eur Heart J. 2008;29:413–421). In addition, in the RIACE cohort, data on hospitalization for heart failure were not as reliable as those on the major acute CVD events that were included in the model (myocardial infarction, stroke, foot ulcer/gangrene/amputation, coronary, carotid, lower limb revascularization, and surgery for aortic aneurysm), as hospital discharge records used for event adjudication did not use consistent definitions. Finally, though heart failure is an important risk factor associated with mortality in diabetic individuals, it is usually the consequence of coronary heart failure, the presence of which is adequately captured by a history of acute myocardial infarction and/or coronary revascularization.

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.

Actually, diabetes duration, HbA1c, and anti-hyperglycemic treatment are only weakly correlated in diabetic patients, especially in those with type 2 diabetes, which is a very heterogeneous condition with wide inter-individuals differences in the rate of progression of metabolic derangement. This is the reason why we cannot include only one and even two terms in Model 2, but we need all three. The same diabetes duration is in fact associated with a wide range of HbA1c values (from normal to very high) and anti-hyperglycemic treatments (from lifestyle only to basal-bolus insulin regimens combined or not with non-insulin agents). Likewise, the same HbA1c value is associated with a wide range of diabetes durations (from newly-diagnosed to long-standing disease) and anti-hyperglycemic treatments or any therapy is associated with a wide range of diabetes durations and HbA1c values.

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.

As stated by the Reviewer, Bonferroni correction was used for ANOVA post-hoc pair-wise comparisons for clinical features, which are important to understand how CVD risk factors and complications/comorbidities distributed across groups.

Regarding correction for multiple comparisons in the survival analysis, we have now compared RHT participants with all the other groups, as stated in our response to point #2. However, according to the primary objective of our study, the only relevant comparison for mortality risk was between RHT and CHT or, when RHT patients were divided based on whether they were or
not on-target, between CRHT and CHT. In this case, adjustment for multiple comparisons is not necessary (please, see Bender & Lange. J Clin Epidemiol. 2001; 54:343–349).

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.

We agree with the Reviewer that the conclusion that less stringent BP goals are needed in high-risk patients with type 2 diabetes seems too radical. However, it was not primarily based on our data, but rather on a large body of previous studies, not dealing with RHT and specifically aimed at testing the hypothesis of the existence of a J-curve effect. Our study may at best support this hypothesis, which however, as clearly stated in our manuscript, is still debated and, as such, by definition requires further investigation. In our study, this hypothesis was simply used to provide an explanation for the findings that hypertensive groups with BP values well below the 130/80 mmHg threshold such as the CHT and CRHT participants had adjusted mortality risks not lower than RHT individuals and even higher than UCRHT individuals, respectively, at variance with data from the general hypertensive population. This has now been clarified in the revised version (please, see page 16, line 10).

Conversely, we believe that the main conclusion of our work, i.e., that RHT is not an independent predictor of death in patients with type 2 diabetes, certainly needs further studies and validation in at least one independent population, since our study is the first analyzing a type 2 diabetes population. This has also been clarified in the revised version (please, see page 16, line 6).

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?

Unfortunately, we have information only on vital status. We do not know if a patient died in hospital and, in case, in which hospital, that could be anyone, especially in large cities like
Rome, Milan, Turin, and Bari, i.e., not necessarily the hospital where the Diabetes Clinic they were attending is located.

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.

The rationale for this analysis was to assess whether the increased mortality risk associated with RHT versus CHT was attributable to the higher BP (and pulse pressure) levels in the former versus the latter group, as now clarified in the revised version (please, see page 8, line 23). The results did not change after adjusting for BP levels, consistent with the findings that the hypertensive groups with BP values well below the 130/80 mmHg threshold such as the CHT and CRHT participants had adjusted mortality risks not lower than RHT individuals and even higher than UCRHT individuals, respectively.

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

We did repeat the analyses by adjusting also for anti-platelet and anti-coagulant treatment. Anti-platelet therapy did not enter the models, whereas anti-coagulant treatment did; in model 3, the HR was 1.49 (95% CI 1.33-1.67, P<0.0001). These data point to a positive independent association of anti-coagulant treatment with mortality that suggests an indication effect, consistent with the finding that use of these agents was highest among RHT participants (8.80%), followed by individuals in the CHT (6.10%), UCHT (3.59%), UTHT (1.30%), and NT (1.13%) group. However, inclusion of these covariates in the models had absolutely no effect of the HRs for the BP status categories.

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.

As requested, we have now provided the median follow-up time (please, see page 10, line 5).
2. Can authors provide number of deaths within each group in Table 1?

The number of deaths cannot be reported in Tables 1, 2, S1, and S2, as they present the baseline clinical features in the RIACE participants with valid information on vital status (stratified by BP status or with resistant hypertension on-target with >4 drugs or not-on target with >3 drugs, according to the 130/80 or 140/90 mmHg BP targets, respectively). The number of deaths is already reported in Table 4 and Supplemental Figure 1.

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

Normotensive or untreated hypertensive individuals were not included as categories in the ANOVA for number of anti-hypertensive drugs and the $\chi^2$ test for number (percent) of patients on-treatment with each class of anti-hypertensive agents.

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.

As stated above (please, see point #2), we have now compared the RHT or CHRT group (reference) with all other groups.

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.

As stated above (please, see point #2), we are now providing results of the comparison between the RHT group and all other groups and, hence, we stated in the Abstract results that “as compared with resistant hypertension, risk for all-cause mortality was significantly lower for all the other groups” instead of “unadjusted hazard ratios were higher for resistant hypertension versus all the other groups” (please, see page 2, line 14).
Reviewer #4

Comments to Author:

This is an interesting study investigating the role of resistant hypertension as an independent risk factor for all-cause mortality in individuals with type 2 diabetes. It is a complicated read and on occasions a little difficult to follow all the acronyms. However, I think that is something that would be very difficult to improve.

We thank the Reviewer for his favorable comments to our paper and agree with him on the difficulty to follow the acronyms, but we could not find an alternative way to identify the different categories.

My main criticism is in the title - as they state in the last sentence of the abstract - "Less stringent BP goals may be preferable in high-risk patients with type 2 diabetes". This seems to contradict the title. The authors would be better adding in an "Is resistant hypertension…..." to the title.

The title has now been changed according to the Reviewer’s suggestion, i.e., “Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study”.

As the authors state management of hypertension is bedevilled with "apparent resistant hypertension" and there will always be issues with medication non-adherence, "white coat hypertension" etc. but this is discussed in the paper.

As stated in the Introduction, cases of “true resistant hypertension” cannot be distinguished from those of “pseudo-resistant hypertension” in population-based studies. As reported by the Reviewer, we have acknowledged among the limitations of our work that “true treatment-resistant hypertension may have been misclassified with pseudo-resistance in a number of cases, as we could not assess adherence and appropriate prescription of anti-hypertensive therapy and to perform ambulatory BP monitoring, the gold standard method for excluding white coat hypertension” (please, see page 15, line 9).

I would take slight issue with the third and fourth sentences of the fourth paragraph of the discussion. The authors cannot presume that treatment of hypertension in patients with untreated or uncontrolled hypertension had been a recent diagnosis and would have been treated aggressively thereafter.
Actually, we cannot prove, but we can at least presume that “patients with untreated or uncontrolled hypertension were likely those with a recent diagnosis of hypertension or not adequately treated, respectively” as stated in the revised version (please, see page 14, line 25). Likewise, we believe that it is reasonable to presume that those hypertensives who were untreated may have received some treatment or that those hypertensives who were uncontrolled on 1 or 2 anti-hypertensive agents may have received at least another drug during the subsequent 10 years of follow-up to achieve BP targets (please, see page 14, line 27). However, this was clearly a speculation to explain why patients with untreated or uncontrolled hypertension had lower mortality risk than those with controlled hypertension, despite higher BP values (please, see page 15, line 2).

I realise that dyslipidaemia and statin therapy would have been included in model 1 but it would have been interesting to know how many patients were on statin therapy.

The number of patients on statin therapy has now been added to all tables, though it almost corresponds to that of patients on lipid-lowering treatment.

The other issue with this study is that the results feel counterintuitively wrong and negative studies can be difficult to publish.

We agree with the Reviewer that negative studies can be difficult to publish, though we believe that the observation that resistant hypertension is not an independent predictor of death beyond target organ damage in patients with type 2 diabetes is an important finding, which can be of interest for the readership of a medical journal.