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

Authors:

Anna Solini (anna.solini@med.unipi.it)
Giuseppe Penno (pgiuse@immr.med.unipi.it)
Emanuela Orsi (emanuela_orsi@yahoo.it)
Enzo Bonora (enzo.bonora@univr.it)
Cecilia Fondelli (c.fondelli@ao-siena.toscana.it)
Roberto Trevisan (rtrevisan@asst-pg23.it)
Monica Vedovato (monica.vedovato@aopd.veneto.it)
Franco Cavalot (franco.cavalot@unito.it)
Olga Lamacchia (olga.lamacchia@unifg.it)
Marco Baroni (marco.baroni@uniroma1.it)
Antonio Nicolucci (nicolucci@coresearch.it)
Giuseppe Pugliese (giuseppe.pugliese@uniroma1.it)

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Author’s response to reviews:

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Lin Lee, PhD
Editor-in-Chief
BMC Medicine

Dear Dr. Lee:
Please find enclosed a revised version of the manuscript # BMED-D-18-01647R1 entitled “Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study”, co-authored by Anna Solini, Giuseppe Penno, Emanuela Orsi, Enzo Bonora, Cecilia Fondelli, Roberto Trevisan, Monica Vedovato, Franco Cavalot, Olga Lamacchia, Marco Baroni, Antonio Nicolucci, and Giuseppe Pugliese, for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group, which we would like to be considered for publication in BMC Medicine.

This paper has been revised according to the additional issues raised by Reviewer #2, which we found very useful for improving our manuscript. Changes are outlined in red. We have also addressed all these issues in a point-by-point rebuttal.

Briefly, we have:

1. mentioned the primary hypothesis and specified the reference population group in the introduction;

2. updated the statistical plan by mentioning that we have compared all the other hypertensive phenotypes and the normotensive group with the RHT (or CRHT) category as reference;

3. discussed in the rebuttal the appropriateness of the interpretation that the resistant hypertension did not predict death;

4. discussed in the rebuttal the reasons for not including anti-platelet and anti-coagulant therapy among covariates and for not presenting the corresponding results;

5. added in the main manuscript precise comments similar to our response to previous Reviewer’s major comment #7.

We hope that you will find this further revised version suitable for publication in BMC Medicine, and I am personally grateful to you for your careful review.

Looking forward to hearing from you soon.
Reviewer #2:

The authors have satisfactorily responded to the earlier feedback. However, there are few points which if clarified in the manuscript will be helpful in affirmation of what the authors described in detail:

We thank the Reviewer for the overall positive judgement and the useful suggestions.

1. Based on response to point #2, the three specific points that can be addressed are:

a. It seems the primary interest of the authors was to determine the association of resistant hypertension with mortality compared to controlled hypertension after adjusting for the factors. However, the authors do not mention this primary hypothesis in the introduction or the statistical plan. The last sentence in the introduction: "The present analysis aimed at …." do not specify the reference population group.

As suggested by the Reviewer, we have now clarified in the Introduction section that, to assess “whether resistant hypertension at baseline is an independent predictor of subsequent death from any cause in individuals with type 2 diabetes from the RIACE cohort”, which is the primary objective of our study, “individuals without hypertension or with non-resistant hypertension were compared with patients with resistant hypertension as reference group” (please, see page 5, line 17).

b. It will be helpful if the authors update the statistical plan as mentioned in the point "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".

We agree with the Reviewer on the importance of updating the statistical plan to clarify that, in all the Cox proportional hazards regression models, the RHT (or CRHT) category served as reference group and to explain the reason for that. Thus, in the Statistical Analysis section, we have now added that “In all the above analyses, the RHT (or CRHT) category was used as reference to allow comparison of the RHT (or CRHT) group with all other groups, i.e., NT and
the various non-RHT groups (and UCRHT), thus distinguishing patients with CHT from those with UTHT or UCHT, who might include RHT individuals” (please, see page 9, line 2).

c. While the change in analytical plan simplified between group comparisons, the interpretation that the resistant hypertension did not predict death may not be appropriate considering the resistant hypertension is the reference group.

As now stated in the Introduction section, “The present analysis aimed at assessing whether resistant hypertension at baseline is an independent predictor of subsequent death from any cause in individuals with type 2 diabetes from the RIACE cohort. To this end, we compared individuals without hypertension or with non-resistant hypertension with patients with resistant hypertension as reference group” (please, see page 5, line 17).

Thus, the aim of the study does remain the assessment of whether resistant hypertension is an independent predictor of death in patients with type 2 diabetes, as previously shown in the general hypertensive population. However, as now stated in the Statistical Analysis section, the analytical plan with resistant hypertension as the reference group was used to allow comparison of resistant hypertension with multiple groups, including not only patients without hypertension, but also different groups with non-resistant hypertension (please, see page 9, line 2). In fact, as stated in the Discussion section, a strength of our paper is “the separation of individuals with untreated or uncontrolled hypertension from those with controlled hypertension, among participants without resistant hypertension”, as some of the patients with untreated or uncontrolled hypertension may have fallen into the resistant hypertensive category when treatment was started or intensified (please, see page 14, line 27).

We believe that changing the interpretation of our data from “resistant hypertension did not predict death beyond target organ damage” to something like “adjusted mortality risk associated with controlled hypertension was not significantly lower than that associated with resistant hypertension” would be misleading. Indeed, though these two conclusions are consistent with each other, the former directly refers to the main objective of the study, whereas the latter reflects only the statistical approach used to handle multiple comparisons.

2. Response to minor comments Methods # point 2, the points of concern are:

a. "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)”. Did the authors select the covariates prior, or some selection method was used?

As stated in the Methods section, we included age, gender, and all CVD risk factors and complications/comorbidities as covariates (please, see page 8, line 18), i.e., we did not make a selection. We did not include anti-platelet and anti-coagulant therapy among covariates because
prescription of these agents is strongly correlated with CVD risk factors and, particularly, complications, with a potential problem of multicollinearity. In this view, the finding that anti-platelet therapy did not enter the models, whereas anti-coagulant therapy did, is not surprising, as 40% of the cohort was on the former treatment (including virtually all patients with a history of CVD), but only 4% was on the latter treatment (i.e., much less than the percentage of individuals with a history of CVD, who were 23% of the cohort).

b. In spite of final model not being significant, inclusion of these factors seem important especially with increased hazards for mortality.

We did repeat the analyses by adjusting also for anti-platelet and anti-coagulant therapy only in order to answer to a specific Reviewer’s question. However, due to the risk of collinearity and, more importantly, the absolute lack of effect of the introduction of these covariates on the HRs for the BP status categories, we believe that we should maintain the originally selected covariates, which are the same as in all the other RIACE publications.

3. Response to major comment #7, the point of concern is:

a. The author's response is not clearly reflected in the manuscript. The authors should add precise comments similar to their response in the main manuscript.

The Reviewer’s major comment #7 was “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 answered that:

a. The conclusion that less stringent BP goals are needed in high-risk patients with type 2 diabetes 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, which our study at best supported and 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.

b. 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 analysing a type 2 diabetes population.

Therefore, we changed the conclusions accordingly, by stating that:
a. Both these findings (i.e., that resistant hypertension did not predict death beyond the increased burden of target organ damage characterizing this condition and that risk of death was higher in individuals with controlled resistant hypertension than in those with uncontrolled resistant hypertension) are at variance with data from the general hypertensive population and require confirmation in other cohorts of patients with type 2 diabetes.

b. The demonstration of a J-curve phenomenon in our cohort further supports the concept that less stringent BP goals may be preferable in individuals with type 2 diabetes, especially in those at high CVD and renal risk, though this issue is still a matter of debate.

Thus, we believe that we did already add the required comments in the manuscript, though in a concise manner. However, to comply with the Reviewer’s request and to further clarify this issue, we have now included two additional sentences in the Discussion section, i.e.:

a. “Though not originally designed to address this issue, our study provides further supports to the existence of a clinically meaningful J-curve effect, which may have increased mortality risk among individuals with controlled hypertension, thus masking the excess risk associated with resistant hypertension” (please, see page 14, line 21).

b. “A further limitation is that our main finding that resistant hypertension is not an independent predictor of death beyond target organ damage cannot be generalized until validated in at least one independent type 2 diabetes population” (please, see page 16, line 1).

Reviewer #4:

I believe that all the points have answered and the paper is ready for publication.

We thank the Reviewer for his favorable comments to our revised manuscript.