Author’s response to reviews

Title: Resistant Hypertension and Cardiovascular Disease Mortality in the US: Results from the National Health and Nutrition Examination Survey (NHANES)

Authors:

Katerina Kaczmarski (kkaczma4@jhmi.edu)
Stephen Sozio (ssozio@jhmi.edu)
Jingsha Chen (jchen206@jhu.edu)
Yingying Sang (ysang1@jhu.edu)
Tariq Shafi (tshafi@jhmi.edu)

Version: 1 Date: 26 Jan 2019

Author’s response to reviews:

Response to Reviewer comments for BNEP-D-17-00616 "Resistant Hypertension and Cardiovascular Disease Mortality in the US: Results from the National Health and Nutrition Examination Survey (NHANES)"

Dear Editor,

Thank you for your thoughtful and considerable efforts to improve our manuscript. We have attempted to address all major reviewer concerns and believe our manuscript is now ready for further review and consideration.

We would also like to note that we updated our analyses with the latest version of NHANES datasets which became available after the initial submission on October 23, 2017. The key change in the analytic sample is that baseline antihypertensive medication data is available for additional participants. As a result, the sample size increased from 6,195 to 6,357 as less participants are excluded due to missing data on antihypertensive medications. We have updated the manuscript to reflect those changes. Results are overall unchanged but with larger sample size the confidence intervals are narrower and p values smaller.

Reviewer comments are in bold and our responses are in italics. Updated parts of the manuscript are in blue font color.

Sincerely,
The Authors

Reviewer 1

1.1. The authors excluded uncontrolled non-aTRH; however, they do not provide a clear explanation of why this group of patients were excluded from the study. I suggest the authors provide a clearer rationale for their reason in excluding this group.

Response: We excluded those with uncontrolled BP (≥140/90 mm Hg) treated with <3 medications as, based on the current definitions, these patients are not considered to have “resistant” hypertension, which was the focus of our paper. The patients with uncontrolled non-aTRH may also have higher risk of cardiovascular mortality but we wanted to maintain the focus our manuscript on those with aTRH. We have added this information to the manuscript.

We further excluded persons with inadequately treated uncontrolled hypertension defined as BP ≥140/90 mm Hg and use of <3 antihypertensive medications because these patients are not considered to have aTRH based on current definitions of treatment resistant hypertension.

1.2. The potentially higher risk of CV death in the aTRH group could be due to the differences in BP, as observed in Table 1 (SBP for any non-TRH was 122 while SBP for any aTRH was 146) and Table 2 (the HR for controlled aTRH vs controlled non-TRH was not statistically significant).

Response: We agree with the reviewer that the systolic BP was higher in the aTRH group. This difference is mainly driven by the higher BP in the uncontrolled aTRH group (144 mm Hg). The controlled aTRH group’s average BP was lower (122 mm Hg). It is quite possible that the difference in outcomes observed between aTRH and non aTRH could be due to BP or its consequences such as chronic kidney disease. This is suggested by the models in Table 2. In Model 2 (age, sex, race adjusted) and Model 3 (further adjusted for BMI, diabetes, smoking, CVD, cholesterol, and CRP), the association with CVD mortality is statistically significant. The association becomes non-significant in Model 4 after addition of eGFR and albuminuria. Both of these factors, eGFR and albuminuria, are in the causal pathway between BP and CVD mortality and the lowering of HR after adjusting for these variables suggests mediation. This is an important point that needs further discussion. We have added a paragraph in the discussion highlighting these points. We thank the reviewer for this important comment.

Discussion

The observed associations between aTRH and cardiovascular mortality in our study provides some interesting insights (Table 2). In the unadjusted model (Model 1), aTRH was associated with a 2.5-fold higher risk of cardiovascular mortality, compared to the non-aTRH group. Adjusting for age, sex, and race (Model 2) reduces the magnitude of this association, reflecting
the confounding effects of these variables. The association is further attenuated by adjusting for additional confounders in Model 3, in particular baseline diabetes and cardiovascular disease which had higher prevalence in the aTRH group as compared to the non-aTRH group. In Model 4, adjusting for kidney function (estimated glomerular filtration rate and albuminuria), further attenuates the association. It is likely that some of these adjustment factors, such as baseline cardiovascular disease and kidney function mediate the observed association between aTRH and outcomes. The higher systolic BP in the aTRH group (144 mm Hg) as compared to the non-aTRH group (122 mm Hg) could be contributing to higher prevalence of cardiovascular and kidney disease noted at the baseline in the aTRH group (Table 1). At baseline 40.1% of those in the aTRH group had cardiovascular disease, compared to 18.9% in the non-aTRH group. Similarly, the aTRH group had lower estimated glomerular filtration rate (68 ml/min|1.73 m2) as compared to the non-aTRH group (82 ml/min|1.73 m2). Clinical implication of these findings is that in patients with aTRH (whether controlled or uncontrolled) careful attention must be paid to reducing cardiovascular risk and preserving kidney function. From a population health perspective, aTRH identifies a patient population at 2.5-fold higher risk of cardiovascular mortality. This high-risk population can be easily identified using electronic health records and population health management strategies could target this population for focused interventions such as lifestyle modification, and use of medications with cardioprotective and renoprotective effects.

1.3. In Table 1, suggest including specific prevalence of use of specific antihypertensive classes among the different patient groups.

Response: We have added this information to the manuscript.

Methods

Antihypertensive medication use was self-reported, and antihypertensive medications were classified as diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and others according to classification codes provided with the NHANES data.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-aTRH</th>
<th>aTRH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Non-aTRH</td>
<td>Non-aTRH Subgroups</td>
<td>Any aTRH</td>
</tr>
<tr>
<td>&lt;3 medications</td>
<td>3 medications</td>
<td>Controlled</td>
</tr>
</tbody>
</table>

Definition: BP mm Hg and number of antihypertensives

- <140/90 AND ≤3
- <140/90 AND <3
- <140/90 AND 3
- =140/90 AND ≥3
- >140/90 AND ≥4
- ≥140/90 AND ≥3

We have added this information to the manuscript.
<table>
<thead>
<tr>
<th></th>
<th>4835 (9.8%)</th>
<th>3837 (7.5%)</th>
<th>998 (9.9%)</th>
<th>1522 (9.9%)</th>
<th>432 (9.9%)</th>
<th>1090 (9.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unweighted Population (N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics, N (%)</strong></td>
<td>2333 (46.3%)</td>
<td>1512 (37.5%)</td>
<td>821 (83.5%)</td>
<td>1310 (86.8%)</td>
<td>404 (93.5%)</td>
<td>906 (83.9%)</td>
</tr>
<tr>
<td><strong>ACE-i or ARB, N (%)</strong></td>
<td>2563 (63.4%)</td>
<td>1862 (59.8%)</td>
<td>701 (77.9%)</td>
<td>1115 (83.2%)</td>
<td>370 (89.3%)</td>
<td>745 (80.2%)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers, N (%)</strong></td>
<td>1348 (24.5%)</td>
<td>890 (20.2%)</td>
<td>458 (43)</td>
<td>892 (56.6%)</td>
<td>283 (65.1%)</td>
<td>609 (53)</td>
</tr>
<tr>
<td><strong>Beta blockers, N (%)</strong></td>
<td>1555 (34.6%)</td>
<td>997 (29)</td>
<td>558 (58.1%)</td>
<td>991 (66.6%)</td>
<td>326 (77.2%)</td>
<td>665 (62)</td>
</tr>
<tr>
<td><strong>Other, N (%)</strong></td>
<td>481 (8)</td>
<td>281 (5.7)</td>
<td>200 (17.5)</td>
<td>624 (38.1)</td>
<td>211 (45.9)</td>
<td>413 (34.7)</td>
</tr>
</tbody>
</table>

1.4. In the discussion, the authors should mention differences in CVD and diabetes between the non-TRH and aTRH groups, and how these may have affected the results. Additionally, this finding is not completely surprising given that aTRH tend to be 'sicker' and have more comorbidities.

Response: We agree with the reviewer and have added this information in the discussion as outlined in response to comment # 1.2 above.


Response: We have added these references and expanded the paragraph where we discussed previous studies on this topic.

1.6. Table 1, for 'Total Cholesterol', the results appear to be in mmol/L, however, the table states that it is in 'mg/dL'. Suggest clarifying this in the table.

Response: The reviewer is correct that the results are in mmol/L. We corrected the units in Table 1.

1.7. The limitations paragraph in the Discussion appears to be lacking; suggest the authors to include additional limitations of the study (i.e., use of cross-sectional surveys which make it difficult for longitudinal follow-up).

Response: We have revised this section and added additional limitations.
Discussion

Several limitations of our study also deserve mention. First, we only had participant reported prescriptions and did not have information on prescription adherence which limits our ability to differentiate between true treatment-resistant hypertension and uncontrolled hypertension as the result of medication noncompliance. Second, medications are assessed at a single timepoint due to the cross-sectional nature of NHANES. A time-updated analysis could account for changing patterns of comorbidities, medications, and BP over time and may find different associations. Third, we did not have information on medication doses. Physician prescription patterns, such as the use of low dose combination antihypertensive medications, may incorrectly assign participants to the aTRH category and bias the observed associations. Fourth, we only assessed cardiovascular mortality and did not have information on cardiovascular events. These limitations of our study are balanced by its strengths including its large sample size representative of the U.S. population, prospective design, inclusion of racial/ethnic minorities, broad age range, rigorous data collection and extensive information on covariates, large number of events, and near-complete mortality follow-up using the NDI. The results of our study are generalizable to non-institutionalized U.S. adults.

Reviewer 2

2.1. Was any information on medication doses from participants collected? If it was not, then it needs to be mentioned in the methods and also in the limitations of the study as inadequate dosing could cause participants to move from one category to another and would bias the results.

Response: We did not have medication dose information. We have added this as a limitation. The revised limitation section is presented below.

Discussion:

Several limitations of our study also deserve mention. First, we only had participant reported prescriptions and did not have information on prescription adherence which limits our ability to differentiate between true treatment-resistant hypertension and uncontrolled hypertension as the result of medication noncompliance. Second, medications are assessed at a single timepoint due to the cross-sectional nature of NHANES. A time-updated analysis could account for changing patterns of comorbidities, medications, and BP over time and may find different associations. Third, we did not have information on medication doses. Physician prescription patterns, such as the use of low dose combination antihypertensive medications, may incorrectly assign participants to the aTRH category and bias the observed associations. Fourth, we only assessed cardiovascular mortality and did not have information on cardiovascular events. These limitations of our study are balanced by its strengths including its large sample size representative of the U.S. population, prospective design, inclusion of racial/ethnic minorities, broad age range, rigorous data collection and extensive information on covariates, large number
of events, and near-complete mortality follow-up using the NDI. The results of our study are generalizable to non-institutionalized U.S. adults.

2.2. In the results section in the subsection of baseline participant categories, the baseline differences between participants without aTRH and with TRH has been mentioned. After that section the baseline differences between the subgroups of non aTRH and those in the subgroups of TRH should also be mentioned

Response: We have added this information to the manuscript.

Results:

Baseline characteristics were similar between aTRH subgroups. Notably, the controlled aTRH subgroup had a greater percentage of participants with prior CVD (48.5% vs. 36.4%), defined as prior heart attack, congestive heart failure, or stroke. Compared to non-aTRH patients on <3 medications, patients on 3 medications were more likely to have diabetes (32.4% vs. 22.7%), prior CVD (31.4% vs. 15.9%), and a prescription for a diuretic (83.5% vs. 37.5%).

2.3. In the results section on the subsection of aTRH and Risk of Cardiovascular Mortality. Last paragraph where the adjusted models has been discussed.

a. Please rephrase the second last sentence where the higher risk of CV mortality was noted in the subgroups of aTRH compared to non-aTRH gropus. Current language is not very clear

Response. We modified this section and hope it is clearer. Please note that with our updated analyses using the most recent version of NHANES datasets, the sample size has increased resulting in narrower confidence intervals and smaller p values. We have updated all our results.

Results:

Similarly, aTRH subgroups had a higher risk of cardiovascular mortality in comparison to the non-aTRH group: controlled aTRH [1.66 (1.03-2.68)] and uncontrolled aTRH [1.43 (1.05-1.94)].

b. The last sentence about non-aTRH subjects that had higher CV mortality with 3 medications compared to those with <3 medications, it needs to be mentioned that the findings while almost significant was not statistically significant. (this also needs to be rephrased in the first paragraph of the "Discussion" section).

Response: We have updated this section. The results are now statistically significant.

Adjusted to the following in the Results:
Among non-aTRH subjects, those on 3 antihypertensives had a trend toward greater risk of cardiovascular mortality than those on <3 antihypertensives [1.35 (0.98-1.86)] (Table 3).

Adjusted to the following in the Discussion:

Among participants without aTRH, those on 3 antihypertensive medications had a trend toward higher risk of cardiovascular mortality than those on <3 antihypertensive medications.

2.4. In the results section on subgroup analysis, no need to mention about the subjects treated with diuretics. You can only mention those that were significant in this section.

Response. We deleted this information.

Results

Pre-specified subgroup analyses are presented in Table 3. Due to multiple comparisons, a p-interaction of <0.005 (p=0.05/10) is suggested as a significant value. Using this threshold, there were no significant differences within subgroups. Among subjects treated with diuretics, the risk of cardiovascular mortality was higher in participants with aTRH than in non-aTRH participants [1.41 (0.98-2.02), p=0.06]. The p-interaction, however, was not statistically significant (p-interaction, 0.48).