Author’s response to reviews

Title: Persistence with Antihypertensives in Uncomplicated Treatment-naïve Very Elderly Patients: A Nationwide Population-based Study

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Author’s response to reviews:

Dear editor

Thank you for reviewing our manuscript and your thoughtful comments. Based on your comments, we revised our manuscript and answers to your comments are as below.

We really appreciate your comments, which could improve the quality of our manuscript.

Followings are reviewers’ comment and our reply to the points raised by the reviewers’ careful consideration listing the corresponding changes made in the manuscript. We’ve marked our reply in blue.

Again, thank you for your time and consideration.
Reviewer 1:

1. Abstract: Lines 40-41: please report the figures of the very elderly and elderly in comparison with which group. It is not self explanatory in the abstract, but was explained in the methods section in the main text, that it was in comparison with the adult group.

Answer: We appreciate the reviewer’s advice. This study was designed to compare the treatment persistence and adherence to antihypertensive medication among the three age cohorts; the very elderly, the elderly and the adults, which was explained in the method part of the Abstract. According to the reviewer’s comment, we revised the sentence to describe that the comparison was assessed among the three age cohorts as below.

Line 40-42: “The treatment persistence and adherence rates over the first year were the lowest in the very elderly (59.5% and 62.8%, respectively) and highest in the elderly (65.2% and 67.9%, respectively) patients among the three age cohorts (p<0.001).”

2. Introduction: Elaborate more on why medication persistence may differ between Western and Asian populations (line 76-77)

Answer: Thank you for the meaningful comments. According to the reviewer’s opinion, we revised this paragraph to describe this issue in more detail as below.

Line 75-80: “The patterns of medication persistence in Asian population may differ from those in Western countries because of differences in race, healthcare systems, and socioeconomic environment [14, 15]. Different racial and ethnic groups show diverse perceptions and attitudes towards health and medicines, which may affect adherence to therapy [16]. Various reimbursement coverages, drug prices, and financial barriers depending on country-specific healthcare system and socioeconomic environment have been reported to affect medication persistence [14, 15, 17].”
3. Results: It is sufficient to present results in one decimal point.

Answer: As recommended by the reviewer, we revised the figures to one decimal place throughout the text including abstract and table.

4. Line 166: the authors state that dyslipidemia was the least common in the very elderly. Table 1 shows that depression was the least common?

Answer: We appreciate the reviewer for pointing this out. For clarification, we revised the corresponding sentences as below.

Line 171-173: “Compared with the other two cohorts, the very elderly cohort had the highest proportion of dementia patients and lowest proportion of patients with dyslipidemia (p<0.0001).”

Reviewer 2:

1. How was hypertension diagnosed, were office readings confirmed by ambulatory or home readings-if not it might suggest that some of the reasons for discontinuation were because of postural hypotension in patients who had white coat hypertension rather than sustained hypertension.

Answer: We agree with the reviewer about the influence of the data for diagnosing hypertension. However, the Health Insurance Review and Assessment Service (HIRA) claims data used in this study did not provide information related to the blood pressure data used for diagnosing hypertension.

Therefore, we defined the hypertensive patients as those with recorded diagnosis code and the use of antihypertensive agent. In addition, to avoid including patients with the wrong diagnosis or prescription error, we excluded patients who had been prescribed only once or less than 7 days
of antihypertensive medication, which might be helpful to exclude the cases of discontinuation due to postural hypotension in patients who had white coat hypertension rather than sustained hypertension.

2. Some extra thought should also be given to reasons the very elderly did not persist with their tablets-this group is more likely to have altered pharmacokinetics and pharmacodynamics compared with the other two with increased adverse events as a result-this fits with the particular problems outlined with beta blockers for example.

Answer: We appreciated the reviewer for in-depth and extensive comments. We agree with the reviewer’s comment and we added this phenomenon to explain the lower persistence rate of the very elderly group in the discussion section as below:

Line 277-279: “The increased risk of adverse drug events and inconsistency in the efficacy associated with changes in pharmacokinetic and pharmacodynamic profiles with aging also may negatively affect drug persistence particularly in the very elderly compared with the elderly patients [36, 37].”

3. It would be helpful to give a brief description in the text about the Charlson Index and in particular how it is scored.

Answer: As recommended by the reviewer, we revised the Method section by including the descriptions about Charlson comorbidity index score as below.

Line 113-116: “The Charlson Comorbidity Index score, a prognostic comorbidity rating score calculated based on 19 disease states each assigned with a score of 1, 2, 3, or 6, corresponding to the risk of mortality, was assessed using the ICD-10 codes to evaluate the patient’s disease burden for 1 year before the index date [19].”
4. It would be very interesting to know whether other tablets were discontinued over the year but perhaps that is beyond the scope of this study. Can you clarify line 231-232?

Answer: We agree with the reviewer and revised the sentences to clarify that one or more comorbidities might induce regular visit to healthcare facilities.

Line 239-241: “These findings may be explained by the fact that very elderly patients with comorbidities might be more likely to continue hypertensive treatment because they require regular visits to healthcare facilities for diseases other than hypertension.”

5. My final point is that even if there were statistically significant differences between groups in persistence and adherence, nonetheless, the treatment adherence was over 60% in all three groups after a year. I would like this point to be made and put in a clinical context.

Answer: Following the recommendation guided by the reviewer, we have added an explanation for the one-year treatment adherence of more than 60% in all three groups in the Discussion section as below.

Line 218-219: “Despite the statistically significant differences in treatment persistence and adherence among the three age cohorts, the one-year treatment adherence was more than 60% in all three groups.”

- The authors' response letter has been included as a supplementary file