PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of combination drugs on antihypertensive medication adherence in a real-world setting: A Korean Nationwide Study
AUTHORS	Kim, Seung Jae; Kwon, Oh Deog; Cho, BeLong; Oh, Seung-Won; Lee, Cheol Min; Choi, Ho-Chun

VERSION 1 - REVIEW

REVIEWER	Burnier Michel Service of Nephrology and Hypertension University Hospital Lausanne Switzerland
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	In this analysis, the authors have compared the adherence to ARBs and CCBs given alone or in combination (free or single pill) in a large group of patients with hypertension followed over 6 years. They analyzed the data essentially according to age and to the number of co-medications. Their results show that adherence is best with single pill combinations than with free combinations of the 2 drug classes or even to monotherapy. The difference in adherence between single pill combination and free drug combination increase with age and with the number of concomitant drugs. Comments: This is an interesting analysis on a very large group of patients followed retrospectively over a 6 year period. Results tend to confirm previous observations indicating that single pill combination has a better adherence than free combinations. 1. The interesting observation is that the single pill combination is better tan an ARB or a CCB alone and this could be discussed specifically. The authors mention that combinations in general are better taken than isolated drugs but this is not obvious in all studies. In this respect it would be important to have data on comorbidities to explain why adherence to a monotherapy is better than to another monotherapy (which contains 2 substances). Patients are not necessarily aware of that. 2.The main issue in this paper is the attribution of the patients to the various groups as shown in figure S3. The reasons to dispatch some patients in one group rather than in another one are not always clear and the reviewer acknowledges that it is a difficult task. Yet, in newly treated patients the critical phase for adherence is the first year. So it would seem reasonable to consider the choice of the first year to select patients. The overall duration on a given regimen may be another strategy. Unfortunately, the dataset does probably not provide the reasons for the changes in therapy. 3. In table1, the authors should indicate the statistical difference between the groups. 4. In this table the comorbidities should be added.

	5. The English should be revised. Some sentences are difficult to understand. For ex. p.7 last sentence: "all single and compound drugs of CCB..."

REVIEWER	MS Kallistratos Asklepeion General Hospital
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	In this study the authors investigated whether single pill combination (SPC) of antihypertensives actually improves adherence using a representative national data. Although the epidemiologic data of Korean hypertensive patients may be of interest, the other data regarding adherence to treatment are already known from several other studies and this study is mainly confirmatory. In addition, the retrospective nature of the study adds significant limitations that are already mentioned from the authors. A minor query, the authors should include a separate more extensive section regarding the limitations of the study.

VERSION 1 – AUTHOR RESPONSE

Response to the Reviewer #1's comments:

1. The interesting observation is that the single pill combination is better than an ARB or a CCB alone and this could be discussed specifically. The authors mention that combinations in general are better taken than isolated drugs but this is not obvious in all studies. In this respect it would be important to have data on comorbidities to explain why adherence to a monotherapy is better than to another monotherapy (which contains 2 substances). Patients are not necessarily aware of that.

We appreciated this excellent comment which points out an important aspect of our study. We also thought that our results demonstrating higher adherence of combination therapies in general than isolated drugs were very interesting since this was not obvious in all studies.

Several studies showed higher adherence of single pill combination therapy compared to monotherapy and reported higher persistence of multiple pill combination therapy being higher than monotherapy. These studies were all cited in the "Discussion" section on page 15.

We explained these results by applying the Health Belief Model, assuming that patients receiving combination therapy tend to have more severe hypertension and they will be more alert to take medications as their physicians prescribed to maintain the targeted blood pressure.

We also agree with you that information of comorbidities of patients are important to explain these results. But while new diseases can be additionally diagnosed at any point in the observation period, a new disease diagnosed at a certain point cannot be considered as having affected the medication adherence of the whole observation period. Therefore, we could only adjust the comorbidities as the average number of diagnoses during the observation period since it would need a highly complicated operationalization to define specific concurrent diseases that reflect a certain point of the observation period. We have added these contents in the "Discussion" section clarifying our view on defining comorbidities as confounding factor more directly in second paragraph of page 19 as below.

“Also, while new diseases can be additionally diagnosed at any point in the observation period, a new disease diagnosed at a certain point cannot be considered as having affected the medication adherence of the whole observation period. That is why we adjusted the comorbidities as the average number of diagnoses”.

2. The main issue in this paper is the attribution of the patients to the various groups as shown in figure S3. The reasons to dispatch some patients in one group rather than in another one are not always clear and the reviewer acknowledges that it is a difficult task. Yet, in newly treated patients the critical phase for adherence is the first year. So, it would seem reasonable to consider the choice of the first year to select patients. The overall duration on a given regimen may be another strategy. Unfortunately, the dataset does probably not provide the reasons for the changes in therapy.

We would like to thank the reviewer for this remarkable comment which points out a significant aspect of our study.

We agree with you that the first year is the critical phase for adherence to the newly treated patients. However, this study was conducted under a slightly different perspective.

It is practically impossible to divide patients into certain drug groups without using operationalization of groups when using real-world data like the NHIS-NSC. This is because medications prescribed to patients can be changed, added or even discontinued during the course of the observation period. The NHIS-NSC data also did not provide the reasons for the changes in therapy just like you mentioned.

We mentioned in the “Method” section that one of the main reasons why we divided the groups according to the last drug taken by the patients was that if the groups were divided according to the initial drug taken, the SPC group may not be selected at all since not many patients start with SPC as the initial therapy unless their hypertension is severe.

That is why we divided the patients to only ARB, only CCB, MPC and SPC group by the last drug taken by the subjects to categorize them without overlapping.

We also thought that comparing average adherence up to maximum of six years was suitable since subjects in our study were not limited to newly treated patients. We have added these contents in the “Discussion” section clarifying the limitation more directly in last paragraph of page 19-20 as below.

“Finally, due to the inevitable limitation of real-world claims data, we could not compare the first year adherence of each group even though the first year is usually an important phase for adherence in newly treated patients. When using real-world data such as the NHIS-NSC used here, it is practically impossible to divide subjects into certain drug groups without implementing some operationalization. This is due to the fact that medications prescribed to patients can be changed, added or even discontinued during the course of the observation period. Moreover, we concluded that categorizing patients into four groups according to the last drug taken by subjects was the most ideal way since not many patients start with SPC as initial therapy unless their hypertension is severe. We also thought that comparing average adherence up to maximum of six years was suitable, since the subjects in our study were not limited to newly treated patients”.

3. In table1, the authors should indicate the statistical difference between the groups.

We have modified the Table 1 to indicate the difference between the groups to reflect your suggestions. Thank you for pointing this out.

4. In this table the comorbidities should be added.

We appreciated this noteworthy comment you gave us.

As we mentioned above in the response of first comment, we adjusted comorbidities as the average number of diagnoses during the observation period and these are included in table 1.

5. The English should be revised. Some sentences are difficult to understand. For ex. p.7 last sentence: "all single and compound drugs of CCB..."

We have revised the English of our manuscript to reflect your suggestions and highlighted the changes made in the manuscript.

Response to Reviewer #2's comments:

1. In this study the authors investigated whether single pill combination (SPC) of

antihypertensives actually improves adherence using a representative national data. Although the epidemiologic data of Korean hypertensive patients may be of interest, the other data regarding adherence to treatment are already known from several other studies and this study is mainly confirmatory. In addition, the retrospective nature of the study adds significant limitations that are already mentioned from the authors. A minor query, the authors should include a separate more extensive section regarding the limitations of the study.

We would like to thank the reviewer for this excellent comment, which has helped us improve our "Discussion" section substantially. We agree with you that this topic has been covered in many previous studies and our findings are mainly confirmatory. However, we believe our study is meaningful that we have confirmed the higher adherence of single pill combination therapy using large scale real-world data despite the limitations caused by retrospective nature of the study.

We have revised our "Discussion" section to clarify our view of the limitation of this study more directly in the page 19-20 as below.

"Moreover, there is a weakness in the analysis regarding adjusting for patients' comorbidities. This study did not specify comorbidities according to severity, and only adjusted with the average number of diagnoses of the subject during the observation period. But in reality, some patients are diagnosed with many mild diseases, while others have few diagnoses but more severe diseases. Also, while new diseases can be additionally diagnosed at any point in the observation period, a new disease diagnosed at a certain point cannot be considered as having affected the medication adherence of the whole observation period. That is why we adjusted the comorbidities as the average number of diagnoses.

Finally, due to the inevitable limitation of real-world claims data, we could not compare the first year adherence of each group even though the first year is usually an important phase for adherence in newly treated patients. When using real-world data such as the NHIS-NSC used here, it is practically impossible to divide subjects into certain drug groups without implementing some operationalization. This is due to the fact that medications prescribed to patients can be changed, added or even discontinued during the course of the observation period. Moreover, we concluded that categorizing patients into four groups according to the last drug taken by subjects was the most ideal way since not many patients start with SPC as initial therapy unless their hypertension is severe. We also thought that comparing average adherence up to maximum of six years was suitable, since the subjects in our study were not limited to newly treated patients".