

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between medical complications according to continuity of care and medication adherence in patients with hypertension in Korea: a national population-based cohort study
AUTHORS	Kim, Dayea; CHA, Jaewoo

VERSION 1 – REVIEW

REVIEWER	Burnier, Michel CHUV, Department of MEdicine, Service of Nephrology and Hypertension
REVIEW RETURNED	17-Mar-2023

GENERAL COMMENTS	<p>The purpose of these analyses was to assess the association of the continuity of care and the adherence level measured during during the first 2 years and teh developement of complications in a large subset of the Korean population included in the national database. As expected, authors confirm that a low continuity of care and a low adherence level is associated with a worse cardiovascular outcome and more cardiovascular event during the next 16 years.</p> <p>Comments</p> <p>This is an interesting clinical question but the paper suffers from several important limitations.</p> <ol style="list-style-type: none">1. The paper is globally very poorly written and the presentation should be improved.2. The definition and characterisation of the various components of the paper are not clearly defined. The methods used to assess COC are superficially described and should be more complete. What parameters are exactly measured ?3. The description of the medical complications should be provided in more details already in the abstract. Which complications? How were complications allocated? which criteria ?4. Persistence to drug therapy was measured to calculate the MPR. This should also be explained in more details: For which drug exactly?5. Terhe are several strange sentences in the results section. For example: "there are more cases of diabetes in the group without diabetes than in the group with diabetes"?? same for cholesterol.6. The description of exclusion criteria should be rewritten7. P.5 the sentence on hypertension progressing caused by coronary heart disease should be rewritten. It is not clear. Same point on line 44-45 of p.5 treatment of hypertension does not cure ! <p>P.7 line 15. the sentence should be rephrased.</p>
-------------------------	--

REVIEWER	Lee, Hyo Young
-----------------	----------------

	Dongseo University, Health Administration
REVIEW RETURNED	27-Mar-2023

GENERAL COMMENTS	<p>1. It would be nice if you could explain the data sources and participants together.</p> <p>2. Generally, paragraph breaks of one or two sentences should be organized as a whole, and the paragraphs should be combined.</p> <p>3. Revise sentence errors in page 7: Methods for measuring COC include Usual Provider Care (UPC), most frequent primary care (MFPC), and modified modified continuity index (MMCI).</p> <p>4. Please move the first paragraph of your research findings to your research methods.: The total number of participants who used the National Health Insurance Service sampling DB from 2002 to 2019 was 102,519 after elimination of patients who had missing data for any of the included variables. No patients were lost to follow-up because not only are all medical records registered through the electronic medical record system, but they are also tracked in accordance with the National Health Insurance Act established by the Korean government, with a follow-up period of 16 years after first 2 years. Data from medical claims were utilized.</p> <p>5. In the result part, combine the research results in one sentence into paragraphs and organize them neatly. These things obscure the quality of the article rather than the essence of the article. Please move away from describing most of the n and % in the table and rearrange the main content. Please make sure to check the pdf file before submitting it.</p> <p>6. Was “Overall hazard ratio according to MPR level” the purpose of the study? Please analyze, present tables, and interpret according to the purpose of the study. And how is MPR measured? A description of this is required in the research method.</p> <p>7. Please present how you divided the categories on page 16 in the research method, and focus on the research result, HR.: In comparison to the excellent medication adherence group (80–100%), the good (60–79%), normal (40–59%), bad (20–39%), and very bad groups (0–19%) had 1.21 (HR=1.21, 95% CI:1.13–1.30), 1.33 (HR=1.33, 95% CI:1.23–1.44),</p> <p>8. How are the highs and lows of the COC level measured and how are they classified? Please explain your research method.</p> <p>9. “MPR was divided into five categories (Excellent=80-100%, Good=60-79%, Normal=40-59%, Bad=20-39%, and Very bad=0-29%)” written in the research results etc. are the contents that should be presented in the research method.</p> <p>10. A total of 11 tables, 5 tables, 3 supplement tables, and 3 figures. It seems that supplement figure 1 should be included in the research subjects part of the research methods. And it seems that the number of tables should be reduced according to the guidelines of this journal and the core contents of the research purpose.</p>
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Comments to the Author):

1. The paper is globally **very poorly written** and the presentation should be improved.

Response: Thank you for your suggestion. The revised manuscript has been edited by an English language editing company. We have acknowledged this in the revised manuscript as follows:

Lines: 448-449

Acknowledgements:

We thank Editage (www.editage.co.kr) for English language editing.

2-) The definition and characterisation of the various components of the paper are not clearly defined. The methods used to assess COC are superficially described and should be more complete. What parameters are exactly measured?

Response: Thank you for your comment. We attempted to include the full description of COC and re-definition and characterisation of the factors. We have added this in our manuscript as follows:

Lines: 186-196

The COC index measures COC on a scale of 0 to 1, based on all visits. The COC index weights both the frequency of visits to each provider and the dispersion of visits between providers. If every visit for medical services to one provider, the COC index will be 1. The formula is:

N = total number of ambulatory care

= number of visits to provider

M = total number of provider

The major drawback of this method is it is not applicable if there are fewer than four visits (23). This is not an ultimate threshold of COC, but is used in practice.

Lines: 242-251

COC was divided into two categories: high (COC index = 1) and low (COC index <1). Most COC-related research in Korea uses this standard because overall levels of COC in Korea is high compared with those in other countries. According to Organization for Economic Cooperation and Development (OECD) statistics on healthcare utilisation, Korea has a three-fold higher outpatient and inpatient medical care use than the OECD average (25). In this study, the mean COC index was 0.811, confirming the high level of COC in Korea. In previous studies the MPR has generally been divided into three categories (>80%, 50–80%, and <50% of MPR) or two categories (>60% and <60% of MPR) (26, 27). However, we decided to use five categories (excellent: 80–100%, good: 60–80%, normal: 40–60%, bad: 20–40%, and very bad: 0–20%) to enable more detailed analysis of the MPR.

3-) The description of the medical complications should be provided in more details already in the abstract. Which complications? How were complications allocated? which criteria?

Response: Thank you for this comment. We explained complications and allocations with exact criteria of hypertensive complications. We have added this in our manuscript as follows:

Lines: 220-224

Medical complications of hypertension—coronary artery disease, vascular complications, cerebrovascular disease, heart disease, and hypertensive nephropathy—were selected based on WHO documentation (1). The WHO documentation also includes cognitive impairment as a type of hypertensive complication, but as data on mental examination was unavailable, we were unable to include cognitive impairment as a complication in our study.

4-) Persistence to drug therapy was measured to calculate the MPR. This should also be explained in more details: For which drug exactly?

Response: Thank you for this important question. We have provided the list of antihypertensive drugs in supplementary table 2 and provided more details on MPR in the manuscript, as follows:

Lines: 200-219

MPR is a common method of measuring medication adherence in general practice. The minimum number of prescriptions is two. The formula for MPR is:

MPR is usually estimated using prescription data, for example, prescription data was provided with the defined daily dose. A MPR value of 1 means complete medication adherence.

The major limitation of MPR estimation is that it is based on retrospective data review, and patients may have received unrecorded medication. However, due to the Korean pharmaceutical information system, unrecorded prescription cannot occur. Another limitation of the MPR method is sharing medicine between family members. However, sharing of medication is likely to be minimal, because each medical appointment is scheduled according to the number of days medication prescribed. The major strength of the MPR method is that research diseases containing data on changeable parameters such as blood pressure (hypertension), HbA1c and fasting blood glucose (diabetes), researchers can closely estimate patient health status based on the drugs that they are prescribed.

Medication adherence refers to the degree of compliance with medications prescribed by a doctor (24). Accurate tracking of prescription data is essential for analysing medication adherence as well as effectively predicting healthcare costs and utilisation (23).

To measure medication adherence, the MPR and proportion of days covered are usually used for analysis (12). We used the COC index and MPR to estimate medication adherence using NHI data, which tracks all prescription data (12). We received professional advice from specialists in internal medicine and cardiology for the selection of antihypertensive drugs (supplementary table 1).

5-) There are several strange sentences in the results section. For example: "there are more cases of diabetes in the group without diabetes than in the group with diabetes"?? same for cholesterol.

Response: Thank you for pointing this out. We have revised the wording as follows:

Lines: 315-317

Patients with diabetes and high cholesterol had a higher incidence of hypertensive complications than patients without diabetes and high cholesterol, respectively.

6-) The description of exclusion criteria should be rewritten.

Response: Thank you for this comment. We have rewritten the description of the exclusion criteria as follows:

Lines: 158-173

To avoid bias, we excluded patients who were prescribed drugs less than twice (n=53,662) to enable proper measurement of the MPR; patients aged <30 years (n=6,630) to exclude low-risk patients; patients who visited medical institutions in 2002 and 2003 (n=54,180) as a washout

period; patients with medical complications (n=5,698) to prevent contamination of results on the incidence of complications; patients who were diagnosed with hypertension from 2016–2019 (n=38,340) to maintain the baseline characteristics of the target population; patients who had taken related drugs or undergone related procedures or surgeries according to the AHRQ guidelines on ambulatory care-sensitive conditions (n=2,047); patients who had visited the medical institution before the index date due to hypertension (n=9,919), or who visited the emergency room or were hospitalised within 2 years of the index date according to the AHRQ guidelines on ambulatory care-sensitive conditions (n=8,907) to avoid unequal baseline characteristics; patients who died within 2 years of the index date (n=1,065) for the washout period of mortality and severity; and patients who visited medical institutions less than four times after the index date (n=22,308) to enable proper measurement of COC. After these exclusions, retrospective data of 102,519 patients (out of 1 million members of the general population of Korea) were included in the analysis (Figure 1).

7-) P.5 the sentence on hypertension progressing caused by coronary heart disease should be rewritten. It is not clear.

Same point on line 44-45 of p.5 treatment of hypertension does not cure !

P.7 line 15. the sentence should be rephrased.

Response: Thank you for these suggestions. We have rewritten the sentences as follows:

Lines: 107-110

Hypertension progresses in approximately 50% of cases caused by coronary artery disease or heart disease, approximately 33% of cases caused by stroke, and 10–15% of cases caused by renal disease (1). It is closely related to cardiovascular disease, which is the leading cause of death worldwide (4).

Lines: 118-119

Early intervention in an outpatient setting slows the onset and progression of the disease (7) and prevents avoidable hospitalisation (5,8).

Lines: 152-157

After excluding patients with missing data for any of the key variables, data on the medical claims of 102,519 patients with hypertension (ICD code= I.10) were extracted from the NHIS database, covering the 2002–2019 period, and included in the analysis. No patients were lost to follow-up because all medical records were registered through the electronic medical record system and tracked in accordance with the National Health Insurance Act established by the Korean government.

Reviewer #2 (Comments to the Author):

1. It would be nice if you could explain the data sources and participants together.

Response: Thank you for this comment. We have revised the methods section as follows:

Lines: 144-157

This study used the data of 1.4 million individuals from the NHIS database from 2002 to 2019 selected using stratified sampling (13). The database, which includes the medical records of more than 50 million people, is stratified by sex and age group (18 strata) (13). To maintain representativeness, sampling was performed according to the demographic characteristics and income quintiles in the Republic of Korea (13). In addition, these cohort data were linked to the national health check-up database of over 66% of the general population

(over 33 million) in Korea. Furthermore, information on the cause of death was provided by linkage to death data from the National Statistical Office (16-17).

After excluding patients with missing data for any of the key variables, data on the medical claims of 102,519 patients with hypertension (ICD code= I.10) were extracted from the NHIS database, covering the 2002–2019 period, and included in the analysis. No patients were lost to follow-up because all medical records were registered through the electronic medical record system and tracked in accordance with the National Health Insurance Act established by the Korean government.

2. Generally, paragraph breaks of one or two sentences should be organized as a whole, and the paragraphs should be combined.

Response: Thank you for pointing this out. We have made changes as follows:

Lines: 277-288

The patient characteristics are shown in supplementary table 2. Of the patients, 51,522 (50.3%) were male, and 50,997 (49.7%) were female. The 50–59-years aged group was the largest age group (30.7%), followed by the aged 60–69-years (24.5%) and 40–49-years (20.7%) age groups. The vast majority of patients (94.0%) were covered by NHI. The largest income categories were the 9th–10th decile (27.0%), followed by the 7th–8th decile (21.5%) and the 5th–6th decile (18.1%). The most common outpatient visit categories were 7–9 visits (29.7%), followed by 10–12 visits (29.5%), and 13 or more visits (25.0%). Of the patients, 50.9% visited only one provider and 31.0% visited two providers.

3. Revise sentence errors in page 7: Methods for measuring COC include Usual Provider Care (UPC), most frequent primary care (MFPC), and modified modified continuity index (MMCI).

Response: Thank you for your comment. We have changed the text as follows:

Lines: 179-180

Methods for measuring COC include the Usual Provider of Care index, most frequent primary care, and the modified modified continuity index (20).

4. Please move the first paragraph of your research findings to your research methods.: The total number of participants who used the National Health Insurance Service sampling DB from 2002 to 2019 was 102,519 after elimination of patients who had missing data for any of the included variables. No patients were lost to follow-up because not only are all medical records registered through the electronic medical record system, but they are also tracked in accordance with the National Health Insurance Act established by the Korean government, with a follow-up period of 16 years after first 2 years. Data from medical claims were utilized.

Response: Thank you for this suggestion. We have moved the paragraph to the methods section and revised it as follows:

Lines: 144-157

This study used the data of 1.4 million individuals from the NHIS database from 2002 to 2019 selected using stratified sampling (13). The NHIS database, which includes the medical records of more than 50 million people, is stratified by sex and age group (18 strata) (13). To maintain representativeness, sampling was performed according to the demographic characteristics and income quintiles in the Republic of Korea (13). In addition, these cohort data were linked to the national health check-up database of over 66% of the general population (over 33 million) in Korea. Furthermore, information on the cause of death was provided by linkage to death data from the National Statistical Office (16-17).

After excluding patients with missing data for any of the key variables, data on the medical claims of 102,519 patients with hypertension (ICD code= I.10) the 2002–2019 period, and included in the

analysis. No patients were lost to follow-up because all medical records were registered through the electronic medical record system and tracked in accordance with the National Health Insurance Act established by the Korean government.

5. In the result part, combine the research results in one sentence into paragraphs and organize them neatly. These things obscure the quality of the article rather than the essence of the article. Please move away from describing most of the n and % in the table and rearrange the main content. Please make sure to check the pdf file before submitting it.

Response: Thank you for this advice. We have shortened the text of the results section to minimise repetition of the results given in the tables, as follows:

Lines 277-288

General characteristics of patients with hypertension

The patient characteristics are shown in supplementary table 2. Of the patients, 51,522 (50.3%) were male, and 50,997 (49.7%) were female. The 50–59-years aged group was the largest age group (30.7%), followed by the aged 60–69-years (24.5%) and 40–49-years (20.7%) age groups. The vast majority of patients (94.0%) were covered by NHI. The largest income categories were the 9th–10th decile (27.0%), followed by the 7th–8th decile (21.5%) and the 5th–6th decile (18.1%). The most common outpatient visit categories were 7–9 visits (29.7%), followed by 10–12 visits (29.5%), and 13 or more visits (25.0%). Of the patients, 50.9% visited only one provider and 31.0% visited two providers. The majority of patients visited clinics (70.8%). The most common comorbidities were dyslipidaemia (49.8%) and diabetes (28.7%). Approximately half the patients (50.9%) had a high level of COC. The majority of patients (55.5%) had an excellent MPR. The most frequent years of diagnosis were 2004 (10.1%), 2005 (12.1%), and 2006 (10.1%).

6. Was “Overall hazard ratio according to MPR level” the purpose of the study? Please analyze, present tables, and interpret according to the purpose of the study. And how is MPR measured? A description of this is required in the research method.

Response: Thank you for this question. We rearranged the content of the manuscript according to the purpose of this study (as shown above) and described the MPR measurement as follows:

Lines: 197-219

MPR is a common method of measuring medication adherence in general practice. The minimum number of prescriptions is two. The formula for MPR is:

MPR is usually estimated using prescription data, for example, prescription data was provided with the defined daily dose. A MPR value of 1 means complete medication adherence.

The major limitation of MPR estimation is that it is based on retrospective data review, and patients may have received unrecorded medication. However, due to the Korean pharmaceutical information system, unrecorded prescription cannot occur. Another limitation of the MPR method is sharing medicine between family members. However, sharing of medication is likely to be minimal, because each medical appointment is scheduled according to the number of days medication prescribed. The major strength of the MPR method is that research diseases containing data on changeable parameters such as blood pressure (hypertension), HbA1c and fasting blood glucose (diabetes), researchers can closely estimate patient health status based on the drugs that they are prescribed.

Medication adherence refers to the degree of compliance with medications prescribed by a doctor (24). Accurate tracking of prescription data is essential for analysing medication adherence as well as effectively predicting healthcare costs and utilisation (23).

To measure medication adherence, the MPR and proportion of days covered are usually used for analysis (12). We used the COC index

and MPR to estimate medication adherence using NHI data, which tracks all prescription data (12). We received professional advice from specialists in internal medicine and cardiology for the selection of antihypertensive drugs (supplementary table 1).

7. Please present how you divided the categories on page 16 in the research method, and focus on the research result, HR.: In comparison to the excellent medication adherence group (80–100%), the good (60–79%), normal (40–59%), bad (20–39%), and very bad groups (0–19%) had 1.21 (HR=1.21, 95% CI:1.13–1.30), 1.33 (HR=1.33, 95% CI:1.23–1.44),

Response: Thank you for this comment. We have explained the categorisation as follows:

Lines: 248-251

In previous studies the MPR has generally been divided into three categories (>80%, 50–80%, and <50%) or two categories (>60% and <60%) (26, 27). However, we decided to use five categories (excellent: 80–100%, good: 60–80%, normal: 40–60%, bad: 20–40%, and very bad: 0–20%) to enable more detailed analysis of the MPR.

8. How are the highs and lows of the COC level measured and how are they classified? Please explain your research method.

Response: Thank you for this question. We have explained our research method as follows:

Lines: 242-247

COC was divided into two categories: high (COC index =1) and low (COC index <1). Most COC-related research in Korea uses this standard because overall levels of COC in Korea is high compared with those in other countries. According to Organization for Economic Cooperation and Development (OECD) statistics on healthcare utilisation, Korea has a three-fold higher outpatient and inpatient medical care use than the OECD average (25). In this study, the mean COC index was 0.811, confirming the high level of COC in Korea.

9. “MPR was divided into five categories (Excellent=80-100%, Good=60-79%, Normal=40-59%, Bad=20-39%, and Very bad=0-29%)” written in the research results etc. are the contents that should be presented in the research method.

Response: Thank you for pointing this out. We have moved the text to the methods section (**Lines 249-251**).

10. A total of 11 tables, 5 tables, 3 supplement tables, and 3 figures. It seems that supplement figure 1 should be included in the research subjects part of the research methods. And it seems that the number of tables should be reduced according to the guidelines of this journal and the core contents of the research purpose.

Response: Thank you for pointing this out. We have thoroughly revised the manuscript and reduced the number of tables and figures.

1

VERSION 2 – REVIEW

REVIEWER	Lee, Hyo Young Dongseo University, Health Administration
REVIEW RETURNED	23-May-2023
GENERAL COMMENTS	1. The background of the study in Abstract should be modified as follows.

	<p>Study settings Secondary data analysis using National insurance claims data at all levels of hospitals in South Korea. This should also be reflected in the research methods part of the text.</p> <p>2. In the “Strengths and limitations of this study” section, a sentence emphasizing new findings from the study must be included.</p> <p>3. In the introduction part, please also present the part about ‘importance and use of COC and MPR’ in one paragraph.</p> <p>4. To use an abbreviation such as NHIS, please write your full name first, then the abbreviation.</p> <p>5. For comorbidity, please suggest how you controlled it in the research method. And if there is comorbidity, describe how it was classified as complication or not.</p>
--	--

VERSION 2 – AUTHOR RESPONSE

Reviewer #2 (Comments to the Author):

The background of the study in Abstract should be modified as follows. Study settings Secondary data analysis using National insurance claims data at all levels of hospitals in South Korea. This should also be reflected in the research methods part of the text.

Response: Thank you for reviewing our manuscript and for your comments. We have responded to all your comments. Our point-by-point response is given below. We hope that the revisions adequately address your concerns.

According to your suggestions, we have made the following revisions to the Abstract and Methods sections:

‘We analysed the secondary data using national insurance claims data at all levels of hospitals in South Korea.’ (Lines 118–119)

‘Secondary data analysis using National insurance claims data at all levels of hospitals in South Korea.’ (Lines 30–31)

In the introduction part, please also present the part about 'importance and use of COC and MPR' in one paragraph.

Response: Thank you for the suggestion. We have explained the importance and use of COC and MPR' in the Introduction of the revised manuscript. The added text is as follows:

'To assess the management of ACSCs in medical institutions, including primary care, COC and MPR are the most important indicators of measurement tools. COC refers to a continuous relationship and consultation between a patient and physician, and the MPR refers to the compliance rate of medications as prescribed by a physician. Therefore, these two measurements are broadly used for the evaluation of the ACSCs management.' (Lines 96–102)

To use an abbreviation such as NHIS, please write your full name first, then the abbreviation.

Response: Thank you for pointing this out. We have edited abbreviations according to your comment as follows:

'This study used the National Health Insurance Service (NHIS) database, in which over 50 million patients are registered (13).' (Lines 104–105)

'We utilised the level of continuity of care (COC) to measure continuity of care and the medication possession ratio (MPR) to measure medication adherence.' (Lines 36–38)

'In an evaluation of all risk factors by the World Health Organization (WHO) and the Global Burden of Disease Study, hypertension ranked first as a contributor to the burden of disease at 20%, with a contribution greater than that of obesity (3).' (Line 79-82)

'Hypertension is also classified as an Ambulatory Care-Sensitive Conditions (ACSCs), which means that early diagnosis and intervention are beneficial in preventing the medical complications that may result in death, hospitalisation, and major medical costs (5).' (Line 86-88)

For comorbidity, please suggest how you controlled it in the research method. And if there is comorbidity, describe how it was classified as complication or not.

Response: Thank you for this comment. We have provided details on the methods that we used to control for comorbidities as follows:

'The term 'comorbidity' indicates that patients or participants have different diseases that can affect the results of the study. Comorbidities are sometimes confused with complications, but comorbidities differ from complications because they do not occur as a result of the target disease. Defining comorbidities plays a pivotal role in risk adjustment because confounding can occur if the results are not adjusted for comorbidities.

In this study, we selected diabetes and dyslipidaemia, which are co-factors of cardiovascular disease, cerebrovascular disease, and hypertensive nephropathy as comorbidities (26-28). These two types of disease could affect the incidence of hypertensive complications.' (Lines 233–240)