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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

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3 **The association between medical complications according to continuity of care and**
4 **medication adherence in patients with hypertension in Korea: a national population-**
5 **based cohort study**
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47 **Conflict of interest**
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49 The authors declare that the research was conducted in the absence of any commercial or
50 financial relationship that could be construed as potential conflicts of interest.
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Abstract

Objectives: To analyse the differences in hypertensive complications according to continuity of care and medication adherence in patients with ambulatory care-sensitive conditions.

Design: A national population-based retrospective cohort study.

Setting: Primary care data at all levels of hospitals in Korea.

Participants: In total, 102,519 patients diagnosed with hypertension were included in this study.

Main outcome measures: The levels of continuity of care (COC) and medication adherence were estimated within the initial 2 years of the follow-up period, and the incidence of medical complications, within the subsequent 16 years. We utilised COC and modified modified continuity index (MMCI), to measure continuity of care, and medication possession ratio (MPR) to measure medication adherence.

Results: Average COC levels in the hypertension group were 0.8112, respectively. The average proportion of MPR in the hypertension group was 73.3%. COC in patients with hypertension showed different results: the low COC (COC<1) group had a 1.14-fold increased risk of medical complications than the high COC (COC=1) group. In terms of MPR in patients with hypertension, the 0–19% MPR group had a 1.5-fold risk of medical complications, the 20–39% MPR group had a 1.42-fold risk of medical complications, the 40–59% MPR group had a 1.36-fold risk of medical complications, and the 60–79% MPR group had a 1.24-fold risk of medical complications relative to the 80–100% MPR group.

Conclusions: In patients with hypertension, high COC and medication adherence for the first 2 years of diagnosis can help prevent medical complications and promote patients' health. Therefore, effective strategies to improve COC and medication adherence are required. Future research will need to consider sensitivity analysis of COC and medication adherence with different study periods.

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5 **Keywords:** Continuity of care, medication adherence, ambulatory care-sensitive conditions,
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8 hypertension, retrospective cohort
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INTRODUCTION

Hypertension is one of the most important health issues worldwide (1). In terms of the global prevalence of hypertension, almost 1.3 billion people, which is close to 20% of the world population, have hypertension (2). The World Health Organization and the Global Burden of Disease Study evaluated the contribution of all risk factors; hypertension ranked first at 20% with a contribution greater than that of obesity (3). Hypertension progresses in approximately 50% of cases caused by coronary artery disease or heart disease, approximately 33% by stroke, and 10–15% by renal disease (1). It is closely related to cardiovascular disease which is the leading cause of death worldwide (4).

Hypertension is also classified as ambulatory care-sensitive conditions (ACSCs) which means that early interventions or diagnosis are beneficial in preventing the progress of medical complications which may result in death, hospitalisation, and huge medical costs (5). ACSCs were classified by the Agency of Health Research and Quality (AHRQ), and the following 16 diseases selected by AHRQ are treated effectively in a timely manner with regards to providing medical services and preventing the occurrence of a disease or in the case of a disease that has already occurred (6). By treating and managing them early, hospitalisation due to aggravation or complications of the disease can be reduced (6). Treatment in the outpatient stage slows the onset and progression of the disease and cures acute and chronic diseases (7). This is known as possible or avoidable hospitalisation (5,8). ACSCs are representative indicators for evaluating the accessibility and quality of primary care (9).

Several studies have focused on hypertension, continuity of care, and medication adherence (10–12). However, the study design was limited to the natural environment and only a small number of patients (10-12) were included. In the data from the National Health Insurance Service (NHIS), over 50 million patients have been registered (13). Patient data

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3 include not only physician visit information but also the prescription data for each visit (13).
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5 Since the National Health Insurance is mandatory for every citizen in Korea, the reliability of
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7 the data is extremely high, and data on the national level of population is stored in big data
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9 centres (NHIS, 2022).
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12 The objective of this study was to analyse the effect of ACSCs provided in a timely
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14 and effective manner and prevent the occurrence of medical complications by treating and
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16 managing early cases of hypertension that have already occurred using continuity of care
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18 (COC) and medication possession ratio (MPR) measurements. Additionally, it aims to
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20 analyse the primary care of ACSCs in different levels of hospitals and their outcomes.
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26 **METHODS**

27 **Inclusion and exclusion of participants**

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29 This study is a national population-based retrospective cohort study and investigated the
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31 incidence of hypertension from 2002.01.01 to 2019.12.31 among the general population in
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33 Korea. Unlike previous studies on the risk of complications according to COC and
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35 medication adherence in the first 2 years, the present study examined the time variance,
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37 including the time of the first visit to the medical institution and patient age (more than 30
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39 years). 14-16 Patients who were prescribed drugs less than two times due to proper
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41 measurement of MPR (Number of excluded participants=53,662), were aged <30 years for
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43 the extraction of higher risk population (Number of excluded participants= 6,630), who
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45 visited medical institutes in 2002 and 2003 (wash-out period, number of excluded
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47 participants=54,180), who had medical complications before the index date due to the
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49 prevention of contamination of results on the incidence (Number of excluded
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51 participants=5,698), who were diagnosed with hypertension from 2016–2019 for maintaining
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53 the baseline characteristics of target population (Number of excluded participants=38,340),
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3 who had taken related drugs or undergone related procedures or surgeries due to the
4 suggestions from AHRQ on ACSCs research (Number of excluded participants=2,047), who
5 had visited the medical institution before the index date due to hypertension to avoid unequal
6 baseline characteristics of patients (Number of excluded participants=9,919), who visited the
7 emergency room or were hospitalized within 2 years of the index date based on the
8 suggestions from AHRQ on ACSCs research (Number of excluded participants=8,907), who
9 died within 2 years of the index date for the washout period of mortality and severity
10 (Number of excluded participants=1,065), and who visited the medical institute less than four
11 times after the index date due to a proper measurement of COC (Number of excluded
12 participants=22,308) were excluded to avoid bias such as misclassification bias or
13 contamination of the results. Finally, 102,519 participants were included in the study from the
14 retrospective data of 1 million members of the general population of Korea [Supplementary
15 Figure 1].
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35 **Measurements**

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37 COC is defined as 'continuance of care by a healthcare provider to meet a patient's medical
38 needs providing high quality and harmonised care (17). Additionally, with a good level of
39 continuous care with doctors, the hospitalisation rate, prevalence rate, and the number of
40 examinations are reduced (18). Methods for measuring COC include Usual Provider Care
41 (UPC), most frequent primary care (MFPC), and modified modified continuity index
42 (MMCI) (19).
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51 Medication adherence refers to the degree of compliance with medications prescribed
52 by a doctor (20). Accurate tracking of prescription data is essential for analysing medication
53 adherence as well as effectively predicting healthcare costs and utilisation (20).
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58 To measure medication adherence, the medication possession ratio (MPR) and proportion of
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3 days covered (PDC) are usually used for analysis (21). We used COC for continuity of care
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5 and MPR to estimate medication adherence using NHI data, which tracks prescription data
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7 completely (12). We received professional advice from doctors of internal medicine or
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9 cardiology for the antihypertensive drug selection [Supplementary Table 1].
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14 **Data sources**

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17 This study used the data of 1 million individuals from the National Health Insurance Service
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19 database (DB) via stratified sampling from 2002 to 2019 (13). The sampling database is
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21 based on the sex and age group (18 sections) of the National Health Information Service DB,
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23 which includes the medical records of more than 50 million people (13). To maintain
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25 representativeness, sampling was performed under the stratification of demographic
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27 characteristics and income quintiles in the Republic of Korea (13). In addition, these cohort
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29 data connected with the national-level health check-up DB of over 66% of general population
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31 (over 33 million) in Korea. Furthermore, information on the cause of death is provided in
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33 connection with death data from the National Statistical Office (22).
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40 **Variables and Statistics**

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42 Factors influencing COC in patients with hypertension and the occurrence of
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44 complications included the sex, age, insurance type, income, outpatient status, COC of the
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46 patient, depending on the number of visits, number of providers, main medical institution,
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48 and comorbidities. Missing values for any valuables were initially eliminated. There was no
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50 lost to follow up because the dataset was based on medical record system and analyzed
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52 retrospectively. Subgroup analysis was performed for primary care because of efficiency of
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54 health system in Korea. Statistical significance was tested for mean and standard deviation
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56 using Student's t-test and analysis of variance. A p-value of <0.05 was regarded to be
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3 statistically significant, and if the assumption was not satisfied, Kruskal, a non-parametric
4 test method, was utilized. In addition, the Wallis test, Wilcoxon rank-sum test, and Fisher's
5 exact test were used.
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10 Depending on the level of COC (COC index low vs. high), observations and
11 differences in results according to independent variables were applied using the chi-squared
12 test.
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17 A comparison of complications according to COC and MPR was performed using
18 Kaplan–Meier survival curves and log-rank tests. The differences in medical complications
19 according to continuity of care and medication adherence were examined. The applied Cox
20 proportional hazards model for incidence was analyzed. The output value of the Cox
21 proportional hazards model is presented as hazard ratios (HRs) and 95% confidence intervals
22 (CIs). Ethics approval for the study was obtained from the Institutional Review Board at
23 Korea University (IRB document no. KUIRB-2021-0333-01). Informed consent was not
24 required due to the retrospective nature of the study. The study has been prepared in
25 accordance with the STROBE guidelines.
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40 **Patient and Public Involvement**

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42 Patients are involved from the time of visiting the medical institute because all medical
43 records were registered for National Health Insurance. Informed consent was not required
44 due to the retrospective nature of the study. All personal data and identifiable information
45 was completely anonymised for retrospective research, with ethics approval from the
46 Institutional Review Board of Korea University.
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56 **RESULTS**

57 **General characteristics of patients with hypertension**

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3 The total number of participants who used the National Health Insurance Service
4 sampling DB from 2002 to 2019 was 102,519 after elimination of patients who had missing
5 data for any of the included variables. No patients were lost to follow-up because not only are
6 all medical records registered through the electronic medical record system, but they are also
7 tracked in accordance with the National Health Insurance Act established by the Korean
8 government, with a follow-up period of 16 years after first 2 years. Data from medical claims
9 were utilized.
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19 In terms of sex, 51,522 (50.3%) patients were men, and 50,997 (49.7%) were
20 women.
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23 In terms of age, we categorized age groups for age stratification. Participants aged
24 50-59 years accounted for the largest share at 30.7%, followed by those aged 60-69 years
25 (24.5%), 40-49 years (20.7%), 70-79 years (15.1%), 30-39 years (5.2%), 80 years or older
26 (3.8%).
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32 Regarding the type of insurance, NHI insurers accounted for the majority (94.0%)
33 followed by other insurance at 6.0%.
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37 The income level was divided into ten sections, which follow the official Korean
38 standard of household income. 9th-10th decile (27.0%), 7th-8th decile (21.5%), 5th-6th
39 decile (18.1%), 1-2 decile (16.5%), over three deciles was followed by the 4th decile
40 (14.9%), and the 0th decile (2.0%).
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46 As for the number of outpatient visits for treatment, 7-9 times were the most
47 frequent at 29.7%, followed by 10-12 times (29.5%), 13 times or more (25.0%), and finally
48 4-6 times (15.8%).
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53 As for the number of providers visited, it includes changes in medical institutes and
54 doctors. 50.9% of the patients visited only one hospital (provider) followed by two places
55 (provider) such as outpatient clinics (31.0%), three places (provider) (12.2%), and four places
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3 (provider) or more (5.9%).
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5 Clinics accounted for 70.8% of major medical institutions, followed by others
6 (9.3%), general hospitals (9.1%), hospitals (6.1%), and tertiary general hospitals (4.7%).
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8 With respect to comorbidities, there were more cases of diabetes in the group without
9 diabetes
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11 (71.3%) than in the group with diabetes (28.7%). Dyslipidemia was also higher in the
12 group without Dyslipidaemia was also higher in the group without dyslipidemia (50.2%) than
13 in that with dyslipidemia (49.8%). The level of COC is divided into a high- level group
14 (COC=1) and a low-level group (COC<1). CoC level accounted for 50.9% of high-level
15 group, followed by low-level group (49.1%).
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26 MPR was divided into five categories (Excellent=80-100%, Good=60-79%,
27 Normal=40-59%,
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30 Bad=20-39%, and Very bad=0-19%). The number of patients with excellent MPR
31 was 55.5%, the highest, followed by good (15.6%), normal (11.5%), bad (9.8%), and very
32 bad (7.6%). The year of diagnosis was also added from 2004 to 2015 [Table 1]. Finally, in
33 terms of year of diagnosis, it accounted for in 2004 (10.1%), 2005 (12.1%), 2006 (10.1%),
34 2007 (8.8%), 2008 (8.9%), 2009 (8.7%), 2010 (7.9%), 2011 (7.6%), 2012 (7.4%), 2013
35 (6.5%), 2014 (5.6%), 2015 (6.4%) [Table 1].
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Table 1. General Characteristics of the Study population

		N	%
Total		102,519	100.0
Sex			
	Male	51,522	50.3
	Female	50,997	49.7
Age			
	30–39	2,084	2.0
	40–49	16,943	16.5
	50–59	15,266	14.9
	60–69	18,532	18.1
	70–79	22,056	21.5
	Over 80	27,638	27.0
Insurance type			
	National Health Insurance	96,325	94.0
	Others	6,194	6.0
Income			
	0 quartile	284	2.0
	1–2 quartile	16,943	16.5
	3–4 quartile	15,266	14.9
	5–6 quartile	18,532	18.1
	7–8 quartile	22,056	21.5
	9–10 quartile	27,638	27.0
Number of visits			
	4–6 times	16,175	15.8
	7–9 times	30,475	29.7
	10–12 times	30,236	29.5
	Over 13 times	25,633	25.0
Number of providers			
	1	52,197	50.9
	2	31,825	31.0
	3	12,462	12.2
	More than 4	6,053	5.9
Levels of hospital			
	Tertiary general hospital	4,857	4.7

	General hospital	9,292	9.1
	Hospital	6,270	6.1
	Clinics	72,612	70.8
	Others	9,488	9.3
CCI Index			
Diabetes			
	Yes	29,391	28.7
	No	73,128	71.3
Dyslipidaemia			
	Yes	51,048	49.8
	No	51,471	50.2
COC level			
	High (COC = 1)	52,179	50.9
	Low (COC > 1)	50,340	49.1
MPR Level			
	Excellent (80-100%)	56,939	55.5
	Good (60-79%)	16,012	15.6
	Normal (40-59%)	11,808	11.5
	Bad (20-39%)	9,996	9.8
	Very bad (0-19%)	7,764	7.6
Year of Diagnosis			
	2004	10,357	10.1
	2005	12,362	12.1
	2006	10,321	10.1
	2007	9,017	8.8
	2008	9,101	8.9
	2009	8,906	8.7
	2010	8,082	7.9
	2011	7,807	7.6
	2012	7,623	7.4
	2013	6,699	6.5
	2014	5,772	5.6
	2015	6,472	6.3

N, Number; CCI, Charlson Comorbidity index; COC, Continuity of Care; MPR, medication possession ratio

Hazard ratio of hypertension complications according to continuity of treatment and adherence to medication in hypertension patients

In participants with hypertension in the low adherence group (COC < 1) compared to the high adherence group (COC = 1) the risk of complications was 1.14 times higher (HR=1.14, 95% CI:1.10–1.17) and statistically significant [Table 2].

Table 2. Overall hazard ratio according to COC level

COC level	Hazard Ratio				
	Patients	Events (N)	IR per 1000PYR	^a HR(95% CI)	<i>p</i> -value
High	52,179	7,143	15.4	Ref	-
Low	50,340	8,142	17.7	1.14(1.10–1.17) ***	<.001

N, Number; COC, continuity of care; HR, hazards ratio; CI, confidence interval; IR, Incidence rate; PYR, Person Years at

Risk

^a Adjusted sex, age, insurance type, income, number of visits, number of providers, level of hospital, and CCI Index

***Significance at $p < .001$; **Significance at $p < .01$.

In comparison to the excellent medication adherence group (80–100%), the good group (60–79%) was 1.24 times (HR=1.24, 95% CI:1.18–1.29), normal group (40–59%) 1.36 times (HR=1.36, 95% CI:1.29–1.42), bad group (20–39%) 1.42 times (HR=1.42, 95% CI:1.35–1.50), and very bad group (0–19%) 1.50 times (HR=1.50, 95% CI:1.42–1.59) at a higher risk of hypertensive complications, and all were statistically significant [Table 3].

Table 3. Overall hazard ratio according to MPR level

MPR Level	Hazard Ratio				
	Patients	Events(N)	IR per 1000PYR	^a HR(95% CI)	<i>p</i> -value

Excellent	56,939	7,143	14.1	Ref	
Good	16,012	2,695	17.9	1.24(1.18-1.29) ***	<.001
Normal	11,808	2,146	19.5	1.36(1.29-1.42) ***	<.001
Bad	9,996	1,834	20.3	1.42(1.35-1.50) ***	<.001
Very bad	7,764	1,467	21.4	1.50(1.42-1.59) ***	<.001

N, Number; MPR, medication possession ratio; HR, hazards ratio; IR, Incidence rate; PYR, Person Years at Risk

^a Adjusted sex, age, insurance type, income, number of visits, number of providers, level of hospital, and CCI Index

***Significance at $p < .001$; **Significance at $p < .01$.

Hazard ratio for each type of hypertension complication according to treatment continuity and medication adherence

COC and medication adherence for the time until complications occurred were analysed.

Kaplan–Meier survival curves analysis was performed [Supplementary Figure 2, Supplementary Figure 3].

Hazard ratio of coronary artery disease

In coronary sinuses in the low continuity group (COC<1) compared to the high COC group (COC=1), the risk of developing pulse disease was 1.10 times higher (HR=1.10, 95% CI:1.03–1.16) and statistically significant.

In comparison to the excellent medication adherence group (80–100%), the good group (60–79%) was 1.26 times (HR=1.26, 95% CI:1.16–1.37), normal group (40–59%) was 1.35 times (HR=1.35, 95% CI:1.23–1.47), Bad group (20-39%) 1.38 times (HR=1.38, 95% CI:1.261.52), and the very bad group (0–19%) 1.38 times (HR=1.38, 95% CI:1.24–1.35) at higher risk of coronary artery disease and all were statistically significant.

Hazard ratio of vascular complications

Vascular summation in the low continuity group (COC<1) compared to that in the high

continuity group (COC=1), the risk of developing the disease was 1.07 times (HR=1.07, 95% CI:0.94-1.23) higher and was not statistically significant.

In comparison to the excellent medication adherence group (80–100%), the good group (60–79%) was 1.25 times (HR=1.25, 95% CI:1.04–1.51), normal group (40–59%) 1.33 times (HR=1.33, 95% CI:1.08–1.63), bad group (20–39%) 1.45 times (HR=1.45, 95% CI:1.17–1.79), and the very bad group (0–19%) 1.59 times (HR=1.59, 95% CI:1.26–2.00) at higher risk of vascular complications and all were statistically significant.

Hazard ratio of cerebrovascular disease

The risk of developing a cerebrovascular disease in the group with low continuity of care (COC<1) compared to the group with high continuity of care (COC=1), was 1.14 times higher (HR=1.14, 95% CI:1.09–1.19) and statistically significant.

In comparison to the excellent medication adherence group (80–100%), the good group (60–79%) was 1.18 times (HR=1.18, 95% CI:1.11–1.26), normal group (40–59%) 1.38 times (HR=1.38, 95% CI:1.29–1.47), bad group (20–39%) was 1.51 times (HR=1.51, 95% CI:1.41–1.62), and very bad group (0–19%) 1.13 times (HR=1.13, 95% CI:1.43–1.67) at higher risk of cerebrovascular disease and all were statistically significant.

Hazard ratio of heart disease

The risk of developing heart disease in the low continuity of care group (COC<1) was 1.11 times higher (HR=1.11, 95% CI:1.06–1.17) compared to the high continuity of care group (COC=1), which was statistically significant.

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), 1.36 (HR=1.36, 95%

CI:1.25–1.48), and 1.47 times (HR=1.47, 95% CI:1.34–1.62) higher risk of heart disease, respectively, and all were statistically significant.

Hazard ratio of hypertensive nephropathy

In patients with hypertension in the low-adherence group (COC<1) compared to the high-adherence group (COC=1) the risk of developing hypertensive nephropathy was 1.05 times higher (HR=1.05, 95% CI:0.95–1.16) and this difference was not statistically significant.

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%) were 1.39 (HR=1.39, 95% CI:1.21–1.60), 1.58 (HR=1.58, 95% CI:1.36–1.84), 1.62 (HR=1.62, 95% CI:1.11–1.89), and 1.62 times (HR=1.62, 95% CI:1.35–1.94) at higher risk of hypertensive nephropathy, respectively and all were statistically significant [Table 4, Table 5].

Table 4. Hazard ratio of medical complications according to COC level

		COC level	
		High	Low
CAD	Events(N)	2,117	2,350
	IR per 1000PYR	4.4	4.9
	^a HR(95% CI)	Ref	1.10 (1.03–1.16) **
	<i>p-value</i>	-	0.002
Vascular complications	Events(N)	412	451
	IR per 1000PYR	0.8	0.9
	^a HR(95% CI)	Ref	1.07 (0.94–1.23)

	<i>p-value</i>	-	0.302
Cerebrovascular disease	Events(N)	3,639	4,178
	IR per 1000PYR	7.6	8.7
	^a HR(95% CI)	Ref	1.14 (1.09–1.19) ***
	<i>p-value</i>	-	<.001
Heart disease	Events(N)	2,602	2,951
	IR per 1000PYR	5.4	6.1
	^a HR(95% CI)	Ref	1.11 (1.06–1.17) ***
	<i>p-value</i>	-	<.001
Hypertensive nephropathy	Events(N)	716	768
	IR per 1000PYR	1.5	1.6
	^a HR(95% CI)	Ref	1.05 (0.95–1.16)
	<i>p-value</i>	-	0.367

N, Number; HR, hazards ratio; CI, confidence interval; COC, continuity of care; CAD,

Coronary Artery Disease; IR, Incidence rate; PYR, Person Years at Risk

^a Adjusted sex, age, insurance type, income, number of visits, number of providers, level of hospital, and CCI Index

***Significance at $p < .001$; **Significance at $p < .01$.

Table 5. Hazard ratio of medical complications according to MPR level

		MPR level				
		Excellent	Good	Normal	Bad	Very bad
CAD	Events(N)	2,081	811	635	535	405
	IR per 1000PYR	4	5.1	5.5	5.6	5.5
	^a HR(95% CI)	Ref	1.26 (1.16–1.37) ***	1.35 (1.23–1.47) ***	1.38 (1.26–1.52) ***	1.38 (1.24–1.53) ***
	<i>p-value</i>	-	<.001	<.001	<.001	<.001
Vascular complications	Events(N)	393	154	120	107	89
	IR per 1000PYR	0.7	1	1	1.1	1.2
	^a HR(95% CI)	Ref	1.25 (1.04–1.51) *	1.33 (1.08–1.63) **	1.45 (1.17–1.79) ***	1.59 (1.26–2.00) ***
	<i>p-value</i>	-	0.018	0.007	0.001	<.001
Cerebrovascular disease	Events(N)	3,613	1,312	1,120	997	775
	IR per 1000PYR	6.9	8.4	9.8	10.6	10.8
	^a HR(95% CI)	Ref	1.18 (1.11–1.26) ***	1.38 (1.29–1.47) ***	1.51 (1.41–1.62) ***	1.54 (1.43–1.67) ***
	<i>p-value</i>	-	<.001	<.001	<.001	<.001
Heart disease	Events(N)	2,585	981	788	659	540
	IR per 1000PYR	4.9	6.2	6.8	6.9	7.4
	^a HR(95% CI)	Ref	1.21 (1.13–1.30) ***	1.33 (1.23–1.44) ***	1.36 (1.25–1.48) ***	1.47 (1.34–1.62) ***
	<i>p-value</i>	-	<.001	<.001	<.001	<.001

	Events(N)	633	278	232	194	147
	IR per 1000PYR	1.2	1.7	2	2	2
Hypertensive nephropathy	^a HR(95% CI)	Ref	1.39 (1.21–1.60) ***	1.58 (1.36–1.84) ***	1.62 (1.38–1.90) ***	1.62 (1.35–1.94) ***
	<i>p-value</i>	-	<.001	<.001	<.001	<.001

N, Number; HR, hazards ratio; CI, confidence interval; MPR, medicine possession rate; CAD, Coronary Artery Disease; IR, Incidence rate; PYR, Person Years at Risk

^a Adjusted sex, age, insurance type, income, number of visits, number of providers, level of hospital, and CCI Index

***Significance at $p < .001$; **Significance at $p < .01$.

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2
3 ***Subgroup analysis of hazard ratio of medical complications according to COC, MPR levels***
4
5 ***in clinics (primary care)***
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8 In patients with hypertension in the low-adherence group (COC<1) compared to the high-
9
10 adherence group (COC=1) the risk of developing medical complications was 1.16 times
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12 higher (HR=1.16, 95% CI:1.12–1.21) and this difference was statistically significant.
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15 In comparison to the excellent medication adherence group (80–100%), the good (60–79%),
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17 normal (40–59%), bad (20–39%), and very bad groups (0–19%) were 1.21 (HR=1.21, 95%
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19 CI:1.15–1.28), 1.37 (HR=1.37, 95% CI:1.29–1.45), 1.43 (HR=1.43, 95% CI:1.34–1.52), and
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21 1.51 times (HR=1.51, 95% CI:1.40–1.61) at higher risk of medical complications,
22
23 respectively and all were statistically significant.
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26 When it comes to the number of visits, 4-6 times compared to 7-9 times, 10-12 times,
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28 and over 13 times of the risk of developing medical complications was 0.86 times (HR=0.86,
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30 95% CI:0.80–0.91), 0.78 times (HR=0.78, 95% CI:0.73–0.83), 0.85 times (HR=0.85, 95%
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32 CI:0.80–0.91) higher and this difference were statistically significant [Supplementary Table
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34 2].
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40 **DISCUSSION**

41
42 This study highlights the fact that the continuity of care and the order of establishing health
43
44 policies can increase response and lower the risk of long-term complications within the first
45
46 two years of diagnosis of hypertension.
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49 In the present study, COC and medication adherence were associated with the
50
51 occurrence of complications caused by hypertension. Overall, for patients with hypertension
52
53 in the low adherence group (COC<1) compared to the high adherence group (COC=1), the
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55 risk of complications was 1.14 times higher and statistically significant. Similarly, with
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57 regards to coronary sinus, cerebrovascular disease, and coronary heart disease, the risk of
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3 developing pulse disease, cerebrovascular disease, and coronary disease, respectively was
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5 greater in the low continuity group than in the high continuity of care group.
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8 In terms of overall medication adherence, in comparison to the excellent medication
9 adherence group (80–100%), the good group (60–79%) was 1.24, 1.26, 1.25, 1.18, 1.21, and
10 1.39 times, normal group (40–59%) 1.36, 1.35, 1.33, 1.38, 1.33, and 1.58 times, bad group
11 (20–39%) 1.42, 1.38, 1.45, 1.51, 1.36, and 1.62 times, and very bad group (0–19%) 1.50, 1.38,
12 1.59, 1.13, 1.47, and 1.62 times at higher risk of hypertensive complications, coronary artery
13 disease, vascular complications, cerebrovascular disease, heart disease, and hypertensive
14 nephropathy, respectively, and all were statistically significant.
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23 This study had several strengths. First, the study obtained population
24 representativeness because national health insurance is mandatory in Korea. Second, medical
25 complications were selected according to the AHRQ standards. Third, this is the first attempt
26 at a long-term (17-year) analysis of ACSCs with medical complications.
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33 However, this study also had several limitations. First, since only the continuity of
34 treatment and medication adherence in the initial 2 years were measured, follow-up after 2
35 years was not reflected in the effects of changes in care. Second, the risk of complications or
36 blood pressure level was not analysed in this study. Third, whether other underlying diseases
37 or external factors may affect the results of this study could not be fully excluded. Fourth, due
38 the retrospective nature of this observational study, recall bias may impact the validity of this
39 study.
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49 There are several policies for the management of ACSCs around the world. For
50 example, policies for diabetes, cervical cancer, and asthma in Australia and policies for
51 depression, cancer, and asthma in the UK and USA; it is possible to provide primary care in a
52 timely manner and manage chronic diseases more efficiently by including more diseases
53 subject to chronic disease management in the ACSCs.
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3 A follow-up study on the differences in the risk of complications according to
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5 changes in care should be conducted in the future.
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10 **Transparency statement**

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12 The lead author affirms that the manuscript is an honest, accurate, and transparent account of
13
14 the study being reported; that no important aspects of the study have been omitted; and that
15
16 any discrepancies from the study as originally planned (and, if relevant, registered) have been
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18 explained.
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24 **SUMMARY BOXES**

25 **What is already known on this topic:**

- 26 • In Ambulatory care-sensitive conditions (ACSC) early interventions or diagnosis are
27
28 beneficial in preventing the progress of medical complications which may result in
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30 death, hospitalisation, and huge medical costs.
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- 33 • Several studies have focused on hypertension, continuity of care, and medication
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35 adherence; however, the study design was limited to the natural environment, and
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37 only a small number of patients were included. Hence this study was conducted using
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39 data from the National Health Insurance Scheme, which is more representative of the
40
41 entire population.
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47 **What this study adds:**

- 48 • In patients with hypertension, a high level of continuity of care and medication
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50 adherence for the first 2 years of diagnosis can have a positive effect on preventing
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52 medical complications and promoting patients' health.
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- 55 • Therefore, effective strategies to improve continuity of care and medication adherence
56
57 are required.
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Data Sharing Statement

Raw data were generated at NHIS (National Health Insurance Services). Derived data supporting the findings of this study are available from the corresponding author Jaewoo Cha on request.

For peer review only

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Supplementary Materials

Supplementary Table 1. Antihypertensive drugs included.

Drugs included
Captopril, enalapril, ramipril, candesartan, fimasartan, losartan, olmesartan, telmisartan, valsartan, carteolol, nadolol, propranolol, nifedipine, felodipine, amlodipine, lercanidipine, CCB, diltiazem, verapamil, atenolol, bisoprolol, celiprolol, metoprolol, amosulalol, carvedilol, bevantolol, doxazosin, terazosin, hydrochlorothiazide, indapamide, furosemide, torsemide, spironolactone, amiloride, hydralazine, minoxidil, nitroprusside

Supplementary Table 2. Subgroup analysis of hazard ratio of medical complications according to COC, MPR levels in clinics (primary care)

	Hazard Ratio				
	Patients	Events(N)	IR per 1000PYR	HR (95% CI)	<i>p-value</i>
COC level					
High	36,273	4,437	13.8	Ref	
Low	36,339	5,405	16.2	1.16(1.12-1.21)***	<.001
MPR Level					
Excellent	41,414	4,674	12.8	Ref	
Good	11,326	1,738	16.1	1.21(1.15-1.28)***	<.001
Normal	7,953	1,362	18.1	1.37(1.29-1.45)***	<.001
Bad	6,518	1,118	18.7	1.43(1.34-1.52)***	<.001
Very bad	5,401	950	19.6	1.51(1.40-1.61)***	<.001
Number of visits					

4~6 times	8,770	1,388	17.8	Ref	
7~9 times	18,484	2,490	15.1	0.86(0.80-0.91)***	<.001
10~12 times	23,493	3,112	14.1	0.78(0.73-0.83)***	<.001
Over 13 times	21,865	2,852	14.9	0.85(0.80-0.91)***	<.001

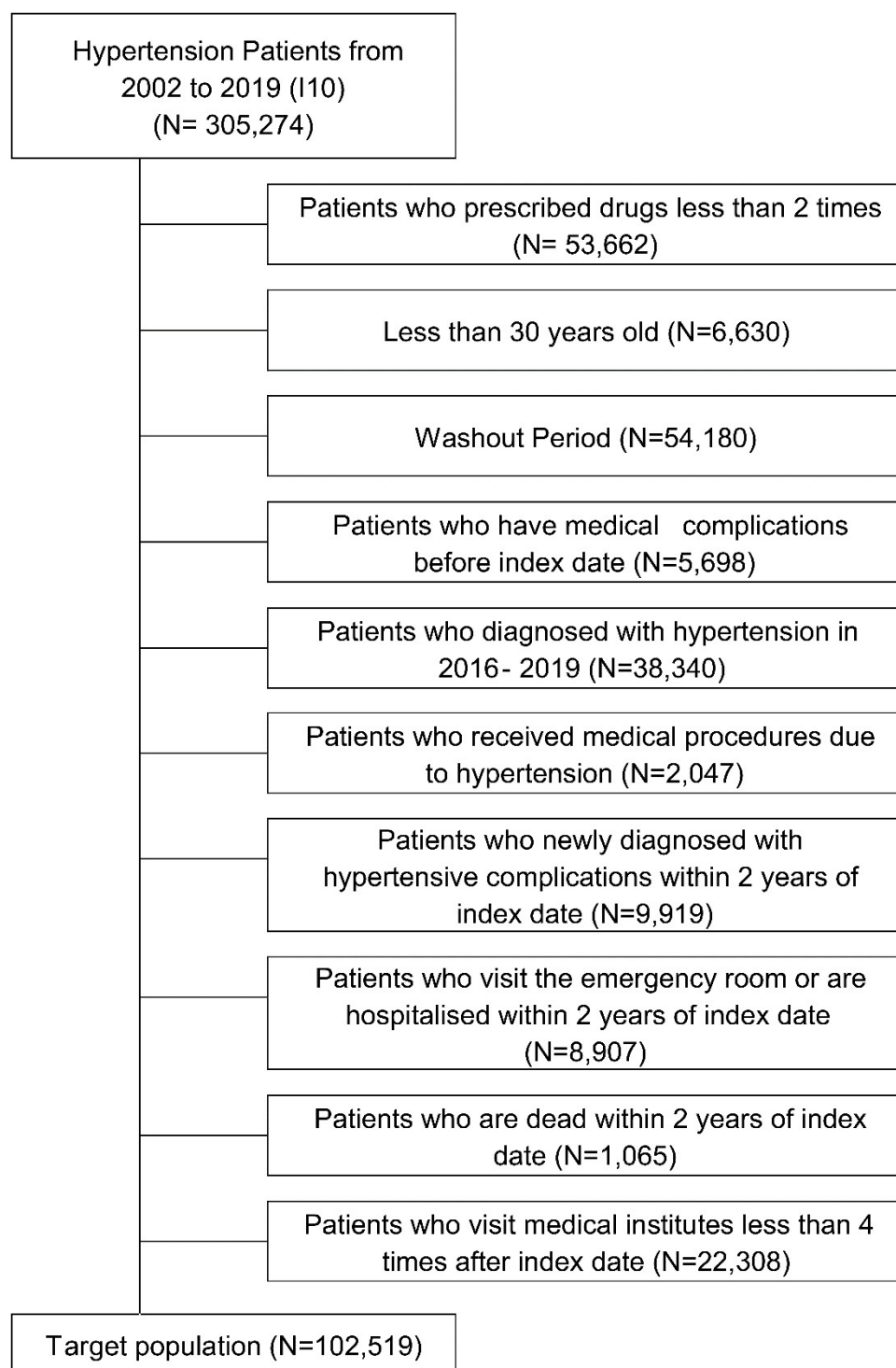
N, Number; COC, continuity of care; MPR, Medication Possession Ratio; HR, hazards ratio; CI, confidence interval; IR,

Incidence rate; PYR, Person Years at Risk

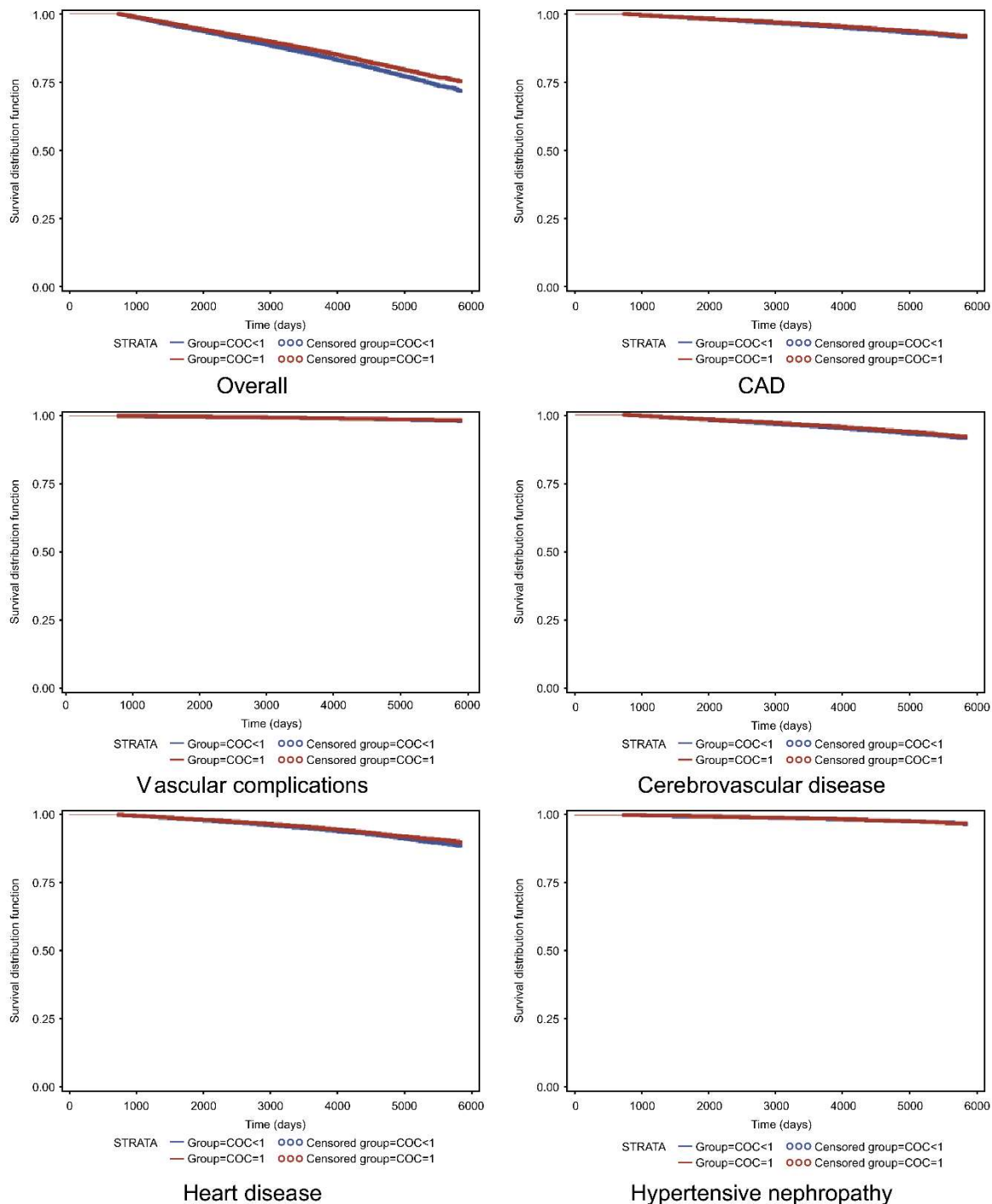
***Significance at $p < .001$.

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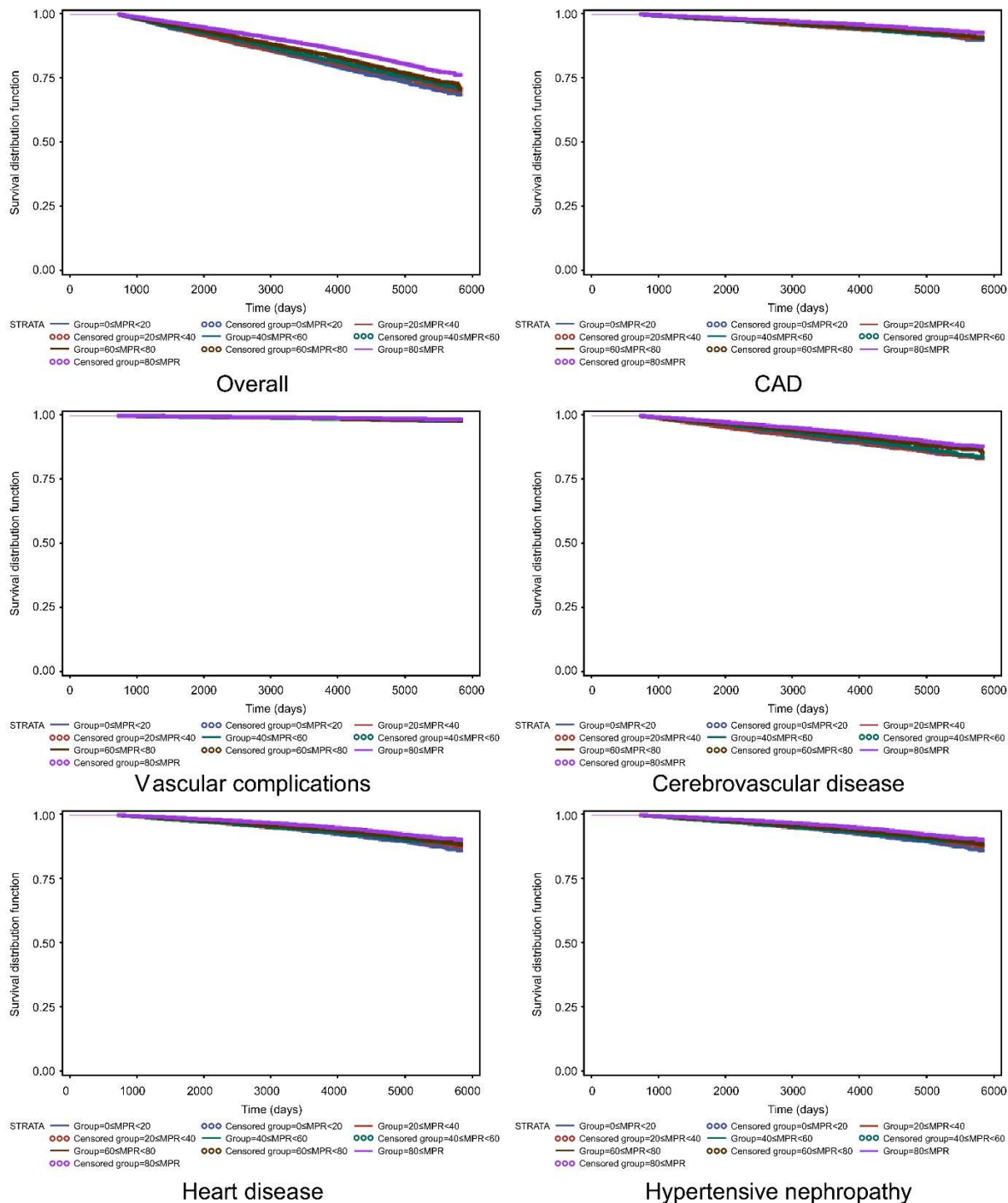
Supplementary Figure 1. Flow diagram of study population



Supplementary Figure 2. Kaplan–Meier Curve of medical complications according to Continuity of Care (COC) level



Supplementary Figure 3. Kaplan–Meier Curve of medical complications according to medicine possession ratio (MPR) level



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-12
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-12
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	12-22
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-22
		(b) Report category boundaries when continuous variables were categorized	12-22
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-22
Discussion			
Key results	18	Summarise key results with reference to study objectives	22-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	23-24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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4 1 **The association between medical complications according to continuity**
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6 2 **of care and medication adherence in patients with hypertension in**
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9 3 **Korea: a national population-based cohort study**
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For peer review only

1
2
3 51 **Abstract**
4

5 52 **Objectives:** To analyse the differences in hypertensive complications according to continuity
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8 53 of care and medication adherence in patients with ambulatory care-sensitive conditions.
9

10 54 **Design:** A national population-based retrospective cohort study.
11

12 55 **Setting:** Medical claims data at all levels of hospitals in Korea.
13

14 56 **Participants:** 102,519 patients diagnosed with hypertension were included in this study.
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16
17 57 **Main outcome measures:** The levels of continuity of care and medication adherence were
18
19 58 estimated within the initial 2 years of the follow-up period, and the incidence of medical
20
21 59 complications within the subsequent 16 years. We utilised a level of continuity of care (COC)
22
23 60 to measure continuity of care and medication possession ratio (MPR) to measure medication
24
25 61 adherence.
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27

28 62 **Results:** The average level of COC in the hypertension group was 0.8112. The average
29
30 63 proportion of MPR in the hypertension group was 73.3%. Continuity of care in patients with
31
32 64 hypertension showed varying results: the low COC group had a 1.14-fold increased risk of
33
34 65 medical complications compared to the high COC group. In terms of a level of medication
35
36 66 adherence in patients with hypertension, the 0–19% MPR group had a 1.5-fold risk of
37
38 67 medical complications relative to the 80–100% MPR group.
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41
42 68 **Conclusions:** In patients with hypertension, high continuity of care and medication adherence
43
44 69 for the first 2 years of diagnosis can help prevent medical complications and promote
45
46 70 patients' health. Therefore, effective strategies to improve continuity of care and medication
47
48 71 adherence are required. Future research should include some factors that may affect the
49
50 72 incidence of hypertensive complications such as familial aggregation, and hazard
51
52 73 stratification by the level of blood pressure were not considered, so there may be residual
53
54 74 confounding and still room for improvement.
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3 76 **Keywords:** Continuity of care, medication adherence, ambulatory care-sensitive conditions,
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5 77 hypertension, retrospective cohort
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8 78

9
10 79 **Strengths and limitations of this study**
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12 80

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14
15 81 • The study had a long follow-up period (18 years) and included over 100,000 participants,
16
17 82 which are regarded as indicators of relatively higher reliability and validity in cohort
18
19 83 studies according to the European Society of Cardiology.
20
21
22 84 • The database we utilised contained data on health service use of over 50,000,000 Korean
23
24 85 citizens' (99.7% of whole population), which means nationally representative.
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26
27 86 • Hypertension (ICD-11 code=I.10) was selected from the ACSCs list in the Agency of
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29 87 Health Research and Quality standard and hypertensive complications were selected
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31 88 according to the World Health Organization and the advice from specialists in internal
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33 89 medicine.
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36 90 • Due to the retrospective nature of the study, the possibility of bias, including
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38 91 misclassification bias, may not be excluded.
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41 92 • Some factors that may affect the incidence of hypertensive complications such as familial
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43 93 aggregation, and hazard stratification by the level of blood pressure were not considered.
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101 INTRODUCTION

102 Hypertension is one of the most important health issues worldwide (1). In terms of the
103 global prevalence of hypertension, almost 1.4 billion people, which is almost 20% of the
104 world population, have hypertension (2). In an evaluation of all risk factors by the World
105 Health Organization and the Global Burden of Disease Study hypertension ranked first as a
106 contributor to the burden of disease at 20%, with a contribution greater than that of obesity
107 (3). Hypertension progresses in approximately 50% of cases caused by coronary artery
108 disease or heart disease, approximately 33% of cases caused by stroke, and 10–15% of cases
109 caused by renal disease (1). It is closely related to ischemic heart disease, which is the leading
110 cause of death worldwide (4).

111 Hypertension is classified as an ambulatory care-sensitive condition, which means that
112 early diagnosis and intervention are beneficial in preventing the medical complications that
113 may result in death, hospitalisation, and major medical costs (5). Ambulatory care-sensitive
114 conditions have been classified by the Agency of Health Research and Quality (AHRQ), and
115 16 diseases selected by the AHRQ can be prevented from progressing if they are treated
116 effectively in a timely manner by providing prevention and medical services (6). By treating
117 and managing these conditions early, hospitalisation due to aggravation or complications of
118 the disease can be reduced (6). Early intervention in an outpatient setting slows the onset and
119 progression of the disease (7) and prevents avoidable hospitalisation (5,8).

120 Ambulatory care-sensitive conditions are representative indicators for evaluating the
121 accessibility and quality of primary care (9). Several studies have focused on hypertension,
122 continuity of care (COC), and medication adherence (10-12). However, the study design of
123 some studies was limited by the setting, and the small number of patients included (10-12).
124 Over 50 million patients are registered in the National Health Insurance Service (NHIS)
125 database (13). Patient data include not only physician visit information, but also the

1
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3 126 prescription data for each visit (13). As National Health Insurance (NHI) is mandatory for
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5 127 every citizen in Korea, the reliability of the data is high, and data are representative of the
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8 128 population on a national level (13).
9

10 129 The objective of this study was to analyse the effect of providing timely and effective
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12 130 ambulatory care to patients with early hypertension on preventing the occurrence of medical
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14 131 complications using COC and the medication possession ratio (MPR) as indicators of
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17 132 effective care. A secondary objective was to assess the outcomes of hypertension according
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19 133 to the level of hospital at which patients were treated.
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23 24 135 **METHODS**

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26 136 This national, population-based, retrospective cohort study investigated the incidence of
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28 137 hypertension from 1 January 2002 to 31 December 2019 among the general population in
29
30 138 Korea. Unlike previous studies on the risk of complications according to the COC and
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32
33 139 medication adherence in the first 2 years, this study examined the time variance, including the
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35 140 time of the first visit to the medical institution and the patient's age (greater than 30 years)
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37 141 (14-15).
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41 42 143 **Inclusion and exclusion of participants**

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44 144 This study used the data of 1.4 million individuals from the NHIS database from 2002 to
45
46 145 2019 selected using stratified sampling (13). The NHIS database, which includes the medical
47
48 146 records of more than 50 million people, is stratified by sex and age group (18 strata) (13). To
49
50 147 maintain representativeness, sampling was performed according to the demographic
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53 148 characteristics and income quintiles in the Republic of Korea (13). In addition, these cohort
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56 149 data were linked to the national health check-up database of over 66% of the general
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58 150 population (over 33 million) in Korea. Furthermore, information on the cause of death was
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3 151 provided by linkage to death data from the National Statistical Office (16-17).
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5 152 After excluding patients with missing data for any of the key variables, data on the
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7 153 medical claims of 102,519 patients with hypertension (ICD code= I.10) were extracted from
8
9 154 the NHIS database, covering the 2002–2019 period, and included in the analysis. No patients
10
11 155 were lost to follow-up because all medical records were registered through the electronic
12
13 156 medical record system and tracked in accordance with the National Health Insurance Act
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15 157 established by the Korean government.
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19 158 To avoid bias, we excluded patients who were prescribed drugs less than twice
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21 159 (n=53,662) to enable proper measurement of the MPR; patients aged <30 years (n=6,630) to
22
23 160 exclude low-risk patients; patients who visited medical institutions in 2002 and 2003
24
25 161 (n=54,180) as a washout period; patients with medical complications (n=5,698) to prevent
26
27 162 contamination of results on the incidence of complications; patients who were diagnosed with
28
29 163 hypertension from 2016–2019 (n=38,340) to maintain the baseline characteristics of the
30
31 164 target population; patients who had taken related drugs or undergone related procedures or
32
33 165 surgeries according to the AHRQ guidelines on ambulatory care-sensitive conditions
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35 166 (n=2,047); patients who had visited the medical institution before the index date due to
36
37 167 hypertension (n=9,919), or who visited the emergency room or were hospitalised within 2
38
39 168 years of the index date according to the AHRQ guidelines on ambulatory care-sensitive
40
41 169 conditions (n=8,907) to avoid unequal baseline characteristics; patients who died within 2
42
43 170 years of the index date (n=1,065) for the washout period of mortality and severity; and
44
45 171 patients who visited medical institutions less than four times after the index date (n=22,308)
46
47 172 to enable proper measurement of COC. After these exclusions, retrospective data of 102,519
48
49 173 patients (out of 1 million members of the general population of Korea) were included in the
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51 174 analysis (Figure 1).
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176 **Measurements**

177 COC was defined as “continuance of care by a healthcare provider to meet a patient's
178 medical needs providing high quality and harmonised care” (18). Additionally, with a good
179 level of continuous care with doctors, the hospitalisation rate, prevalence, and the number of
180 medical visits are reduced (19). Methods for measuring COC include the Usual Provider of
181 Care index, most frequent primary care, and the modified modified continuity index (20).

182 Shortell identified four core factors required for COC (21). First, data should be for
183 individuals. Second, analysed data should be distinguished and comparable when individuals
184 visit different medical institutions and providers. Third, COC should reflect the total number
185 of visits for care. Finally, appropriate referral patterns should also be considered (22). Korea
186 has a fee for service system without a proper referral system (22).

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

$$191 \quad COC = \frac{\sum_{j=1}^M n_j^2 - N}{N(N-1)}$$

192 N = total number of ambulatory care

193 n_j = number of visits to provider

194 M = total number of provider

195
196 The major drawback of this method is it is not applicable if there are fewer than four
197 visits (23). This is not an ultimate threshold of COC, but is used in practice.

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

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$$MPR = \frac{\text{Sum of days' supply for all fills in a period}}{\text{\# of days in period}}$$

5
6 201 MPR is usually estimated using prescription data, for example, prescription data was
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8 202 provided with the defined daily dose. A MPR value of 1 means complete medication
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10 203 adherence.

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13 204 The major limitation of MPR estimation is that it is based on retrospective data review,
14
15 205 and patients may have received unrecorded medication. However, due to the Korean
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17 206 pharmaceutical information system, unrecorded prescription cannot occur. Another limitation
18
19 207 of the MPR method is sharing medicine between family members. However, sharing of
20
21 208 medication is likely to be minimal, because each medical appointment is scheduled according
22
23 209 to the number of days medication prescribed. the major strength of the MPR method is that
24
25 210 research diseases containing data on changeable parameters such as blood pressure
26
27 211 (hypertension), HbA1c and fasting blood glucose (diabetes), researchers can closely estimate
28
29 212 patient health status based on the drugs that they are prescribed.

30
31
32
33 213 Medication adherence refers to the degree of compliance with medications prescribed by
34
35 214 a doctor (24). Accurate tracking of prescription data is essential for analysing medication
36
37 215 adherence as well as effectively predicting healthcare costs and utilisation (23). To measure
38
39 216 medication adherence, the MPR and proportion of days covered are usually used for analysis
40
41 217 (12). We used the COC index and MPR to estimate medication adherence using NHI data,
42
43 218 which tracks all prescription data (12). We received professional advice from specialists in
44
45 219 internal medicine and cardiology for the selection of antihypertensive drugs (Supplementary
46
47 220 table 1).

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51 221 Medical complications of hypertension—coronary artery disease, vascular complications,
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53 222 cerebrovascular disease, heart disease, and hypertensive nephropathy—were selected based
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55 223 on WHO documentation (1). The WHO documentation also includes cognitive impairment as
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224 a type of hypertensive complication (1), but as data on mental examination was unavailable,
225 we were unable to include cognitive impairment as a complication in our study.

226

227 **Statistical analysis**

228 Explanatory variables influencing COC and the occurrence of complications in patients
229 with hypertension included sex, age, insurance type, income, outpatient status, COC, MPR
230 level of the patient, number of visits, number of providers, main medical institution, and
231 comorbidities. Patients with values for any of these variables were excluded. There was no
232 loss to follow-up because the dataset was based on the medical record system and was
233 analysed retrospectively. Subgroup analysis was performed for primary care visits to assess
234 the efficiency of the healthcare system in Korea. The statistical significance of differences
235 between groups was assessed using Student's t-test and analysis of variance. P values <0.05
236 were regarded as statistically significant. The Kruskal–Wallis test and Wilcoxon rank-sum
237 test were used to compare continuous variables that were not normally distributed, and
238 Fisher's exact test was used to compare categorical variables between groups.

239 Insurance type is divided into two categories, Health Insurance beneficiaries and medical
240 aid recipients. The NHI system in Korea enables medical aid recipients to obtain free health
241 services because it is based on the lowest level of household income.

242 Income was divided into ten categories as described in supplementary table 2.

243 COC was divided into two categories: high (COC index =1) and low (COC index <1).
244 Most COC-related research in Korea uses this standard because overall levels of COC in
245 Korea is high compared with those in other countries. According to Organization for
246 Economic Cooperation and Development (OECD) statistics on healthcare utilisation, Korea
247 has a three-fold higher outpatient and inpatient medical care use than the OECD average (25).
248 In this study, the mean COC index was 0.8112, confirming the high level of COC in Korea.

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2
3 249 In previous studies, the MPR has generally been divided into three categories (>80%, 50–
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5 250 80%, and <50% of MPR) or two categories (>60% and <60% of MPR) (26, 27). However,
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8 251 we decided to use five categories (excellent: 80–100%, good: 60–80%, normal: 40–60%, bad:
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10 252 20–40%, and very bad: 0–20%) to enable more detailed analysis of the MPR.

11
12 253 Outpatient status, number of visits, number of providers, main medical institution are
13
14 254 required factors for calculating the COC level. We used the Charlson Comorbidity Index to
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16
17 255 measure comorbidities (28).

18
19 256 Categorical variables associated with the level of COC (low vs high), were compared
20
21 257 using the chi-square test. A comparison of complications according to the COC and MPR was
22
23
24 258 performed using Kaplan–Meier survival curves and log-rank tests. The differences in medical
25
26 259 complications according to COC and medication adherence were examined. The Cox
27
28 260 proportional hazards model was used to compare the risk. Hazard ratios (HRs) and 95%
29
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31 261 confidence intervals (CIs) were estimated using multivariable Cox proportional hazards
32
33 262 regression.

34 35 263 36 37 264 **Ethical issues**

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39 265 Ethics approval for the study was obtained from the Institutional Review Board at Korea
40
41
42 266 University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required
43
44
45 267 due to the retrospective nature of the study. The study has been prepared in accordance with
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47 268 the STROBE guidelines.

48 49 269 50 51 270 **Patient and public involvement**

52
53 271 We did not involve patients and public in this study because it was a retrospective study
54
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56 272 using data from the NHIS database.

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274 **RESULTS**

275 The average continuity of care level in the hypertension group was 0.8112. The average
276 medication possession ratio in the hypertension group was 73.3%.

277 **General characteristics of patients with hypertension**

278 The patient characteristics are shown in supplementary table 1. Of the patients, 51,522
279 (50.3%) were male, and 50,997 (49.7%) were female. The 50–59-years aged group was the
280 largest age group (30.7%), followed by the aged 60–69-years (24.5%) and 40–49-years
281 (20.7%) age groups. The vast majority of patients (94.0%) were covered by NHI. The largest
282 income categories were the 9th–10th decile (27.0%), followed by the 7th–8th decile (21.5%)
283 and the 5th–6th decile (18.1%). The most common outpatient visit categories were 7–9 visits
284 (29.7%), followed by 10–12 visits (29.5%), and 13 or more visits (25.0%). Of the patients,
285 50.9% visited only one provider and 31.0% visited two providers. The majority of patients
286 visited clinics (70.8%). The most common comorbidities were dyslipidemia (49.8%) and
287 diabetes (28.7%). Approximately half the patients (50.9%) had a high level of COC. The
288 majority of patients (55.5%) had an excellent MPR. The most frequent years of diagnosis
289 were 2004 (10.1%), 2005 (12.1%), and 2006 (10.1%).

291 **Risk of complications of hypertension according to the continuity of care level and** 292 **medication adherence**

293 Compared with the high COC group, participants in the low COC group had a
294 significantly higher risk of complications (HR: 1.14, 95% CI: 1.10–1.17) (Table 1).

295

296 **Table 1. Risk of complications of hypertension according to the continuity of care level**

COC level	No. of patients	No. of events	IR per 1000 PYR	HR ^a (95% CI)	<i>p</i>
High	52,179	7,143	15.4	Ref	
Low	50,340	8,142	17.7	1.14 (1.10–1.17)***	<0.001

297 CI, confidence interval; COC, continuity of care; HR, hazard ratio; IR, incidence rate; PYR, person-years at risk

298 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and
299 Charlson Comorbidity Index

300 ***,<0.001

301 Compared with the excellent MPR group, the risk of developing hypertensive
302 complications was significantly higher in the good, normal, bad, and very bad MPR groups
303 (Table 2).

304 **Table 2. Risk of hypertensive complications according to the medication possession ratio**

MPR level	No. of patients	No. of events	IR per 1000 PYR	HR ^a (95% CI)	<i>p</i>
Excellent	56,939	7,143	14.1	Ref	
Good	16,012	2,695	17.9	1.24 (1.18-1.29)***	<0.001
Normal	11,808	2,146	19.5	1.36 (1.29-1.42)***	<0.001
Bad	9,996	1,834	20.3	1.42 (1.35-1.50)***	<0.001
Very bad	7,764	1,467	21.4	1.50 (1.42-1.59)***	<0.001

305 HR, hazard ratio; IR, incidence rate; MPR, medication possession ratio; PYR, person-years at risk

306 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and
307 Charlson Comorbidity Index

308 ***,<0.001

310 **Risk of specific types of hypertension complication according to the continuity of care** 311 **level and medication adherence**

312 Kaplan–Meier survival curves showing the time until complications occurred according to
313 the COC and medication adherence are shown in supplementary figures 1 and 2, respectively.

314 The risks of developing coronary artery disease, vascular complications, cerebrovascular
 315 disease, heart disease, and hypertensive nephropathy according to each COC level and
 316 medication adherence level are shown in tables 3 and 4, respectively. Patients with diabetes
 317 and high cholesterol had a higher incidence of hypertensive complications than patients
 318 without diabetes and high cholesterol, respectively.

319

320 **Table 3. Risk of medical complications of hypertension according to the continuity of**
 321 **care level**

Complication	Parameter	COC level	
		High	Low
CAD	Events (N)	2,117	2,350
	IR per 1000 PYR	4.4	4.9
	HR ^a (95% CI)	Ref	1.10 (1.03–1.16)**
	<i>p</i>	-	0.002
Vascular complications	Events (N)	412	451
	IR per 1000 PYR	0.8	0.9
	HR ^a (95% CI)	Ref	1.07 (0.94–1.23)
	<i>p</i>	-	0.302
Cerebrovascular disease	Events (N)	3,639	4,178
	IR per 1000 PYR	7.6	8.7
	HR ^a (95% CI)	Ref	1.14 (1.09–1.19)***
	<i>p</i>	-	<0.001
Heart disease	Events (N)	2,602	2,951
	IR per 1000 PYR	5.4	6.1
	HR ^a (95% CI)	Ref	1.11 (1.06–1.17)***
	<i>p</i>	-	<0.001
Hypertensive nephropathy	Events (N)	716	768
	IR per 1000 PYR	1.5	1.6

Complication	Parameter	COC level	
		High	Low
	HR ^a (95% CI)	Ref	1.05 (0.95–1.16)
	<i>p</i>	-	0.367

322 CAD, coronary artery disease; CI, confidence interval; COC, continuity of care; HR, hazard ratio; IR, incidence
 323 rate; PYR, person-years at risk

324 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and
 325 Charlson Comorbidity Index

326 **, <.01 ***,<0.001

327 **Table 4. Risk of medical complications of hypertension according to the medication possession ratio**

Complication	Parameter	MPR level				
		Excellent	Good	Normal	Bad	Very bad
CAD	Events (N)	2,081	811	635	535	405
	IR per 1000 PYR	4	5.1	5.5	5.6	5.5
	HR ^a (95% CI)	Ref	1.26 (1.16–1.37)***	1.35 (1.23–1.47)***	1.38 (1.26–1.52)***	1.38 (1.24–1.53)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001
Vascular complications	Events (N)	393	154	120	107	89
	IR per 1000 PYR	0.7	1	1	1.1	1.2
	HR ^a (95% CI)	Ref	1.25 (1.04–1.51)*	1.33 (1.08–1.63)**	1.45 (1.17–1.79)***	1.59 (1.26–2.00)***
	<i>p</i>	-	0.018	0.007	0.001	<0.001
Cerebrovascular disease	Events (N)	3,613	1,312	1,120	997	775
	IR per 1000 PYR	6.9	8.4	9.8	10.6	10.8
	HR ^a (95% CI)	Ref	1.18 (1.11–1.26)***	1.38 (1.29–1.47)***	1.51 (1.41–1.62)***	1.54 (1.43–1.67)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001

Complication	Parameter	MPR level				
		Excellent	Good	Normal	Bad	Very bad
Heart disease	Events (N)	2,585	981	788	659	540
	IR per 1000 PYR	4.9	6.2	6.8	6.9	7.4
	HR ^a (95% CI)	Ref	1.21 (1.13–1.30)***	1.33 (1.23–1.44)***	1.36 (1.25–1.48)***	1.47 (1.34–1.62)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001
Hypertensive nephropathy	Events (N)	633	278	232	194	147
	IR per 1000 PYR	1.2	1.7	2	2	2
	HR ^a (95% CI)	Ref	1.39 (1.21–1.60)***	1.58 (1.36–1.84)***	1.62 (1.38–1.90)***	1.62 (1.35–1.94)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001

328 CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MPR, medication possession ratio; PYR, person-years at risk

329 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and Charlson Comorbidity Index

330 *, < .05; **, <.01 ***,<0.001

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3 331 The risk of coronary artery disease was significantly higher in the low continuity group
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5 332 than the high COC group (HR: 1.10, 95% CI: 1.03–1.16) (Table 3). Compared with the
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7
8 333 excellent MPR group, the risk of coronary artery disease was significantly higher in the good,
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10 334 normal, bad, and very bad MPR groups (Table 4).

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12 335 The risk of vascular complications did not differ significantly according to the COC level
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14 336 (table 3). Compared with the excellent MPR group, the risk of vascular complications was
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16
17 337 significantly higher in the good, normal, bad, and very bad MPR groups (table 4).

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19 338 The risk of cerebrovascular disease was significantly higher in the low continuity group
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21 339 than the high COC group (HR: 1.14, 95% CI: 1.09–1.19) (table 3). Compared with the excellent
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23
24 340 MPR group, the risk of cerebrovascular disease was significantly higher in the good, normal,
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26 341 bad, and very bad MPR groups (table 4).

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28 342 The risk of heart disease was significantly higher in the low COC group than the high COC
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30 343 group (HR: 1.11, 95% CI: 1.06–1.17) (table 3). Compared with the excellent MPR group, the
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33 344 risk of heart disease was significantly higher in the good, normal, bad, and very bad MPR
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35 345 groups (table 4).

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37 346 The risk of hypertensive nephropathy did not differ significantly according to the COC
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39 347 level (table 3). Compared with the excellent MPR group, the risk of hypertensive nephropathy
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42 348 was significantly higher in the good, normal, bad, and very bad MPR groups (table 4).

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46 350 **Subgroup analysis of risk of medical complications according to continuity of care and**
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48 351 **medication possession ratio levels in primary care clinics**

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51 352 A subgroup analysis of the risk of medical complications according to the COC level and
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53 353 MPR in patients with hypertension attending primary care clinics showed that the risk of
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56 354 developing complications was significantly higher in in the the low COC group than the high
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58 355 COC group (HR: 1.16, 95% CI: 1.12–1.21). Compared with the excellent MPR group, the
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3 356 risk of developing hypertensive complications was significantly higher in the good, normal,
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5 357 bad, and very bad MPR groups. Compared with patients who had 4–6 visits, the risk of
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7 358 developing medical complications was significantly lower in patients with 7–9 visits, 10–12
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9 359 visits, or 13 visits or more (Supplementary table 3).

360

361 **DISCUSSION**

362 This study highlights the fact that the COC and order of establishing health policies can
363 increase the response and lower the risk of long-term complications within the first two years
364 of diagnosis of hypertension. In this study, COC and medication adherence were associated
365 with the occurrence of complications caused by hypertension. Overall, for patients with
366 hypertension in the low as compared to the high COC group, the risk of complications was
367 significantly higher. Similarly, the risk of developing coronary artery disease, cerebrovascular
368 disease, and heart disease was greater in the low as compared to the high COC group. In
369 terms of overall medication adherence, in comparison to the excellent medication adherence
370 group (80–100%), the good group (60–79%), normal group (40–59%), bad group (20–39%),
371 and very bad group (0–19%) were at significantly higher risk of developing hypertensive
372 complications such as coronary artery disease, vascular complications, cerebrovascular
373 disease, heart disease, and hypertensive nephropathy.

374 Other COC and MPR studies have found that patients with low medication adherence are
375 more likely to result in progress to inpatient or mortality (HR: 1.24, 95% CI:1.18-1.29). The
376 differences were due to the type of antihypertensive medication, follow-up period, and the
377 differences in the definition of medication adherence. We overcame these limitations because
378 of the 18 years follow-up period.

379 Another MPR study showed that low medication adherence is more likely to result in
380 progress to inpatient or mortality (HR: 1.57, 95% CI:1.40-1.76). this result is similar to that

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3 381 of our study (29).
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5 382 Other COC and MPR studies focused on hypertension and diabetes, and found that for
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7 383 hypertension, low medication adherence and low COC are more likely to result in progress to
8
9 384 death in hospitalised patients (HR: 1.66 (95% CI:1.55-1.77) 1.14(95% CI: 1.08-1.20),
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11 385 respectively). Low medication adherence and low COC are more likely to result in progress
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13 386 to hospitalisation or death among outpatients (HR, 1.67(95% CI:1.47-1.90)). The differences
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15 387 were because the incidence of hypertensive complications were not among their outcomes,
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17 388 and the reason for hospitalisation varied, potentially causing the overestimation of the results.
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21 389 This study had several strengths. First, the study obtained population representativeness
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23 390 because we utilised NHI data and NHI subscription is legally mandatory (covering
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25 391 approximately 99.7%) in Korea. Second, the disease was selected from AHRQ standards of
26
27 392 ACSCs and hypertensive complications were selected according to the WHO. Third, there is a
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29 393 standard in ACSCs related to hypertension (no cardiac procedures included), which is often
30
31 394 omitted in previous studies, and this is the first attempt at a long-term (18-year) analysis of
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33 395 ambulatory care-sensitive conditions (hypertension) with a clearer definition of patients and
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35 396 its incidence rate of complications. However, this study also had several limitations. First, as
36
37 397 only the continuity of treatment and medication adherence in the initial 2 years were
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39 398 measured, follow-up after 2 years was not reflected in the effects of changes in care. Second,
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41 399 the risk of complications or blood pressure level was not analysed in this study. Third,
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43 400 whether other underlying diseases or external factors may affect the results, such as familial
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45 401 aggregation, the levels of blood pressure, and over-prescription of drugs, of this study could
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47 402 not be fully excluded. Fourth, due to the retrospective nature of this observational study,
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49 403 misclassification or recall bias may impact the validity of this study. Finally, this study can be
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51 404 elevated to mortality or factor study. The case-control or prospective cohort study to
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53 405 elucidate the association between COC, MPR levels, and the mortality of patients with
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3 406 hypertensive complications with its characteristics.
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5 407 There are several policies for the management of ambulatory care-sensitive conditions
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7 408 worldwide. For example, there are policies for diabetes, cervical cancer, and asthma in
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9 409 Australia and policies for depression, cancer, and asthma in the UK and USA; it is possible to
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11 410 provide primary care in a timely manner and manage chronic diseases more efficiently by
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13 411 including more diseases subject to chronic disease management in the ambulatory care-
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15 412 sensitive conditions (30). A follow-up study on the differences in the risk of complications
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17 413 according to changes in care should be conducted in the future.
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21 414 This study sheds light on the association between COC and medication adherence and the
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23 415 incidence of hypertensive complications such as coronary artery disease and heart disease.
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25 416 The continuous management of blood pressure can be beneficial to prevent hypertensive
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27 417 complications among the patients with hypertension. The implication should be based on
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29 418 subgroup analysis, visiting medical institutes of primary care is adequately beneficial to
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31 419 patients with hypertension. Therefore, the Korean government should establish health
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33 420 policies related to chronic diseases that need management with a view to long-term care.
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35 421 Moreover, because of its unique structure (lack of a gatekeeper system (referral system)), the
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37 422 healthcare system of the Republic of Korea is facing a financial shortage. Future studies
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39 423 should compare the cost-effectiveness of care provided by different types of medical
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41 424 institutions, such as general hospitals and clinics.
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49 426 **a. Contributorship statement**

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51 427 Conceptualisation: Dayea Kim, Methodology: Dayea Kim, Software: Dayea Kim, Data
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53 428 curation: Dayea Kim, Writing – Original draft preparation: Jaewoo Cha, Visualisation: Jaewoo
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55 429 Cha, Investigation: Dayea Kim, Jaewoo Cha, Supervision: Jaewoo Cha, Validation: Jaewoo
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57 430 Cha, Writing – Reviewing and editing: Dayea Kim, Jaewoo Cha
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3 431
45 432 **b. Competing interests**

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7
8 433 The authors declare that the research was conducted in the absence of any commercial or
9
10 434 financial relationship that could be construed as potential conflicts of interest.

11
12 435
1314 436 **c. Funding**

15
16
17 437 This research received no specific grant from any funding agency in the public, commercial or
18
19 438 not-for-profit sectors.

20
21 439
2223 440 **d. Data sharing statement**

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25
26 441 Raw data were generated by the National Health Insurance Service. Derived data supporting
27
28 442 the findings of this study are available from the corresponding author, Jaewoo Cha, on request.

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30 443
3132 444 **e. Ethics statements**33 445 **Patient consent for publication**

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36 446 Not applicable

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3940 448 **f. Acknowledgements**

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42
43 449 We thank Editage (www.editage.co.kr) for English language editing.

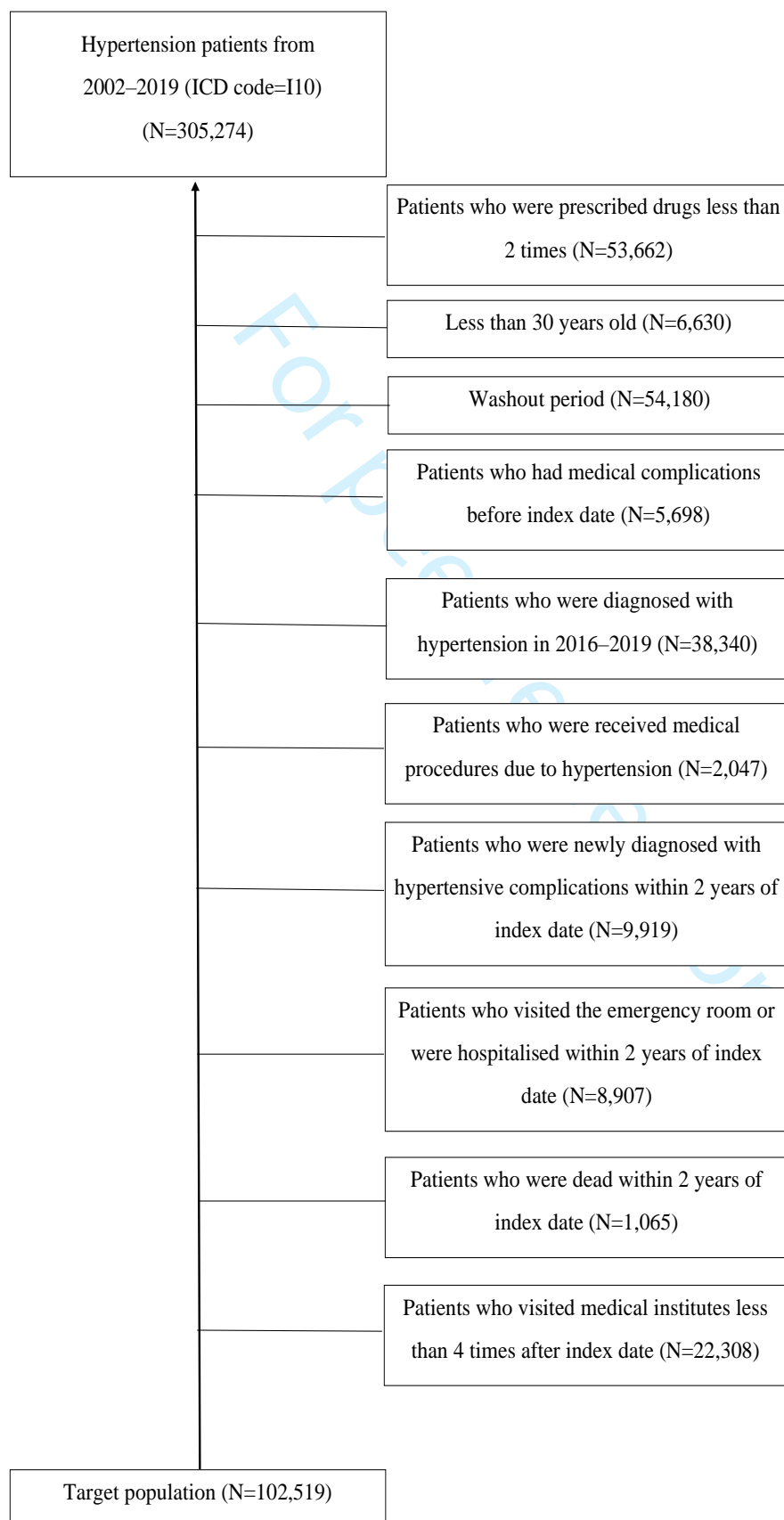
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Figure 1. Flow diagram of the study population

Supplementary Materials

Supplementary Table 1. Antihypertensive drugs included.

Drugs included
Captopril, enalapril, ramipril, candesartan, fimasartan, losartan, olmesartan, telmisartan, valsartan, carteolol, nadolol, propranolol, nifedipine, felodipine, amlodipine, lercanidipine, CCB, diltiazem, verapamil, atenolol, bisoprolol, celiprolol, metoprolol, amosulalol, carvedilol, bevantolol, doxazosin, terazosin, hydrochlorothiazide, indapamide, furosemide, torsemide, spironolactone, amiloride, hydralazine, minoxidil, and nitroprusside.

Supplementary Table 2. General Characteristics of the Study population

Variable		N	%
Total		102,519	100.0
Sex	Male	51,522	50.3
	Female	50,997	49.7
Age	30–39	2,084	2.0
	40–49	16,943	16.5
	50–59	15,266	14.9
	60–69	18,532	18.1
	70–79	22,056	21.5
	Over 80	27,638	27.0
Insurance type	National Health Insurance	96,325	94.0
	Others	6,194	6.0
Income	0 decile (0USD)	284	2.0
	1st and 2nd deciles (857-1,781USD)	16,943	16.5
	3rd and 4th deciles (2,609-3,273USD)	15,266	14.9
	5th and 6th deciles (3,963-4,620USD)	18,532	18.1
	7th and 8th deciles (5,357-6,323USD)	22,056	21.5
	9th and 10th deciles (7,925-11,288USD)	27,638	27.0
Number of visits	4–6	16,175	15.8
	7–9	30,475	29.7
	10–12	30,236	29.5
	≥13	25,633	25.0
Number of providers	1	52,197	50.9
	2	31,825	31.0
	3	12,462	12.2
	≥4	6,053	5.9

Variable		N	%
Level of hospital	Tertiary general hospital	4,857	4.7
	General hospital	9,292	9.1
	Hospital	6,270	6.1
	Clinic	72,612	70.8
	Others	9,488	9.3
CCI: Diabetes	Yes	29,391	28.7
	No	73,128	71.3
CCI: Dyslipidaemia	Yes	51,048	49.8
	No	51,471	50.2
COC	High (COC index =1)	52,179	50.9
	Low (COC index < 1)	50,340	49.1
MPR	Excellent (80–100%)	56,939	55.5
	Good (60–79%)	16,012	15.6
	Normal (40–59%)	11,808	11.5
	Bad (20–39%)	9,996	9.8
	Very bad (0–19%)	7,764	7.6
Year of diagnosis	2004	10,357	10.1
	2005	12,362	12.1
	2006	10,321	10.1
	2007	9,017	8.8
	2008	9,101	8.9
	2009	8,906	8.7
	2010	8,082	7.9
	2011	7,807	7.6
	2012	7,623	7.4
	2013	6,699	6.5
	2014	5,772	5.6
	2015	6,472	6.3

COC, continuity of care; MPR, medication possession ratio

Supplementary Table 3. Subgroup analysis of the hazard ratio of medical complications according to COC and MPR levels in clinics (primary care)

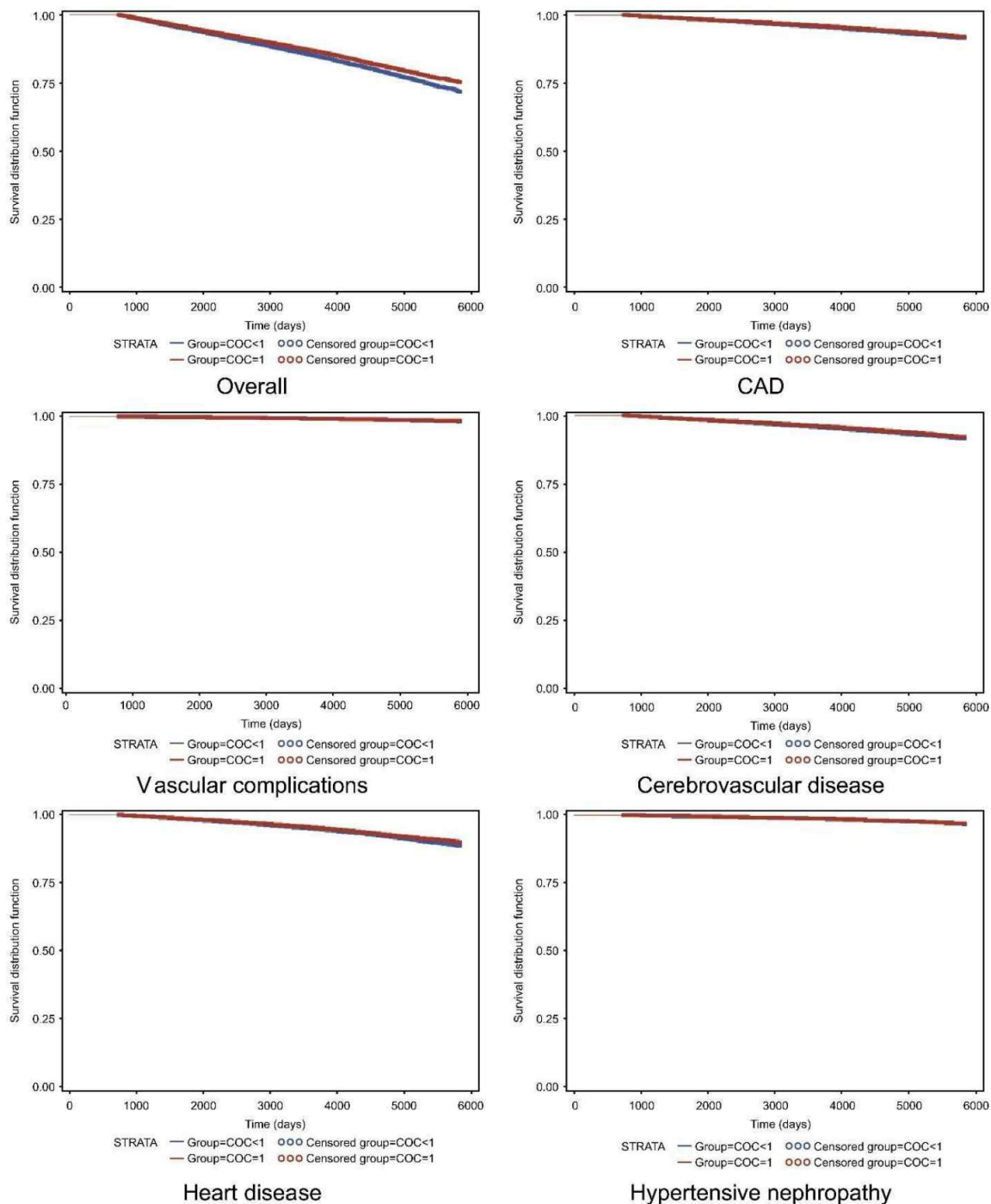
	Hazard Ratio				
	Patients	Events (N)	IR per 1000PYR	HR (95% CI)	<i>p-value</i>
COC level					
High	36,273	4,437	13.8	Ref	
Low	36,339	5,405	16.2	1.16 (1.12–1.21)***	<.001
MPR Level					
Excellent	41,414	4,674	12.8	Ref	
Good	11,326	1,738	16.1	1.21 (1.15–1.28)***	<.001
Normal	7,953	1,362	18.1	1.37 (1.29–1.45)***	<.001
Bad	6,518	1,118	18.7	1.43 (1.34–1.52)***	<.001
Very bad	5,401	950	19.6	1.51 (1.40–1.61)***	<.001
Number of visits					
4–6 times	8,770	1,388	17.8	Ref	
7–9 times	18,484	2,490	15.1	0.86 (0.80–0.91)***	<.001
10–12 times	23,493	3,112	14.1	0.78 (0.73–0.83)***	<.001
Over 13 times	21,865	2,852	14.9	0.85 (0.80–0.91)***	<.001

N, Number; COC, continuity of care; MPR, Medication Possession Ratio; HR, hazards ratio; CI, confidence interval; IR,

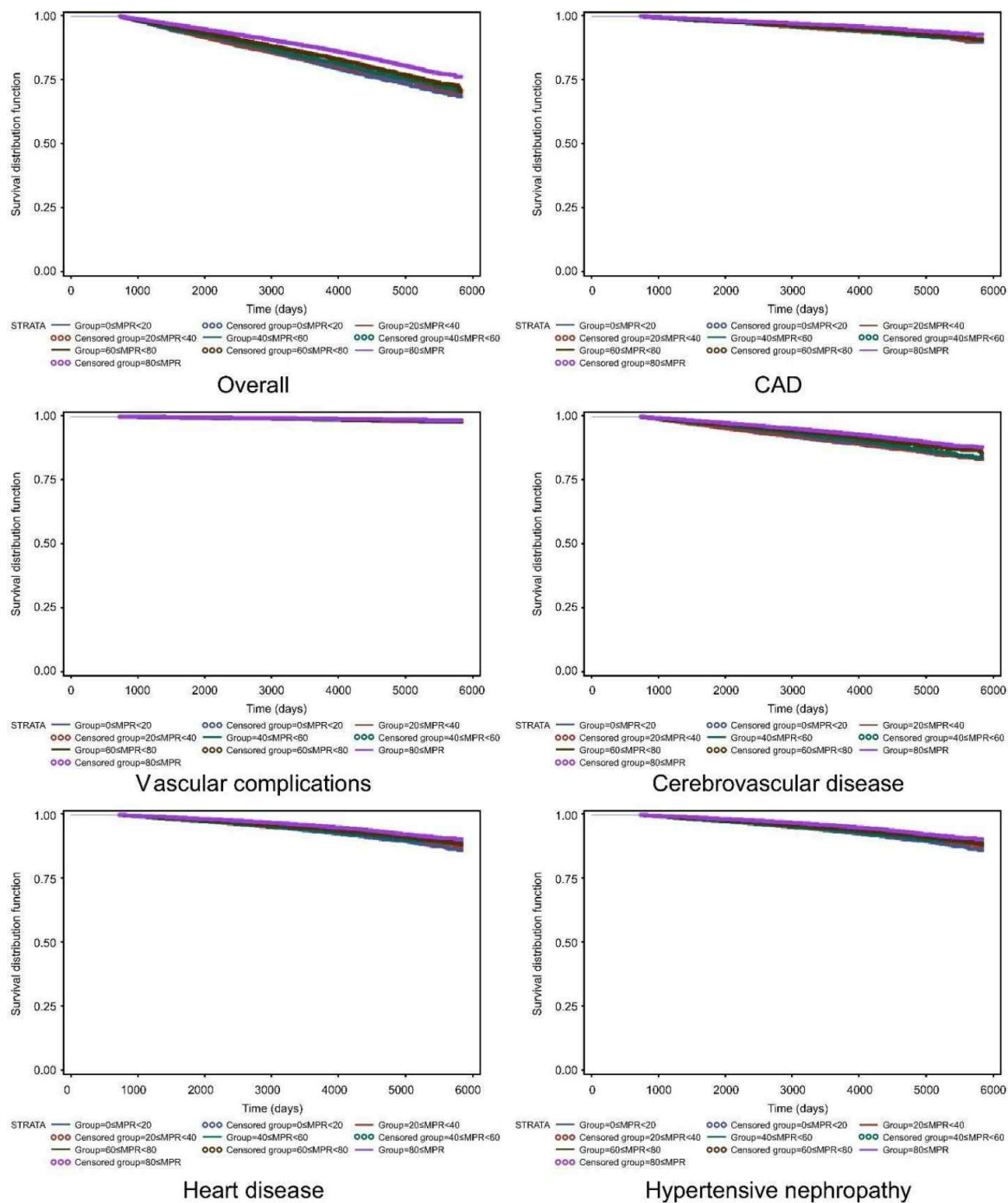
Incidence rate; PYR, Person Years at Risk

***Significance at $p < .001$.

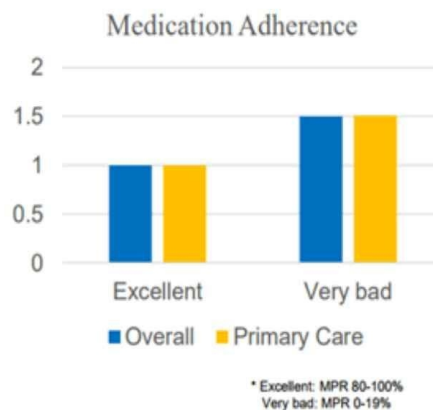
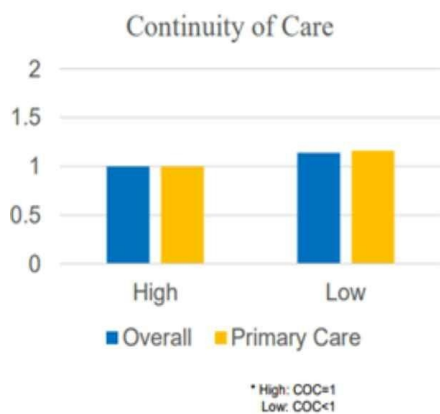
Supplementary Figure 1. Kaplan–Meier Curve of medical complications according to Continuity of Care (COC) level



Supplementary Figure 2. Kaplan–Meier Curve of medical complications according to medicine possession ratio (MPR) level



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-12
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10-11
		(b) Describe any methods used to examine subgroups and interactions	10
		(c) Explain how missing data were addressed	7
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-14
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	12-19
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-19
		(b) Report category boundaries when continuous variables were categorized	12-19
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-19
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18-19
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

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3 1 **The association between medical complications according to continuity of care and**
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5 2 **medication adherence in patients with hypertension in Korea: A national population-**
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7 3 **based cohort study**
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52
53 23 others meeting the criteria have been omitted.
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3 26 **ABSTRACT**
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5 27 **Objectives:** To analyse the differences in hypertensive complications according to continuity
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8 28 of care and medication adherence in patients with hypertension.

9
10 29 **Design:** A national population-based retrospective cohort study.

11
12 30 **Setting:** Secondary data analysis using National insurance claims data at all levels of hospitals
13
14
15 31 in South Korea.

16
17 32 **Participants:** A total of 102,519 patients diagnosed with hypertension were included in this
18
19 33 study.

20
21 34 **Primary outcome measures:** The levels of continuity of care and medication adherence were
22
23 35 estimated within the initial 2 years of the follow-up period, and the incidence of medical
24
25 36 complications was estimated within the subsequent 16 years. We utilised the level of continuity
26
27 37 of care (COC) to measure continuity of care and the medication possession ratio (MPR) to
28
29 38 measure medication adherence.

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31
32
33 39 **Results:** The average level of COC in the hypertension group was 0.8112. The average
34
35 40 proportion of the MPR in the hypertension group was 73.3%. Continuity of care in patients
36
37 41 with hypertension showed varying results: the low COC group had a 1.14-fold increased risk
38
39 42 of medical complications compared to the high COC group. In terms of the level of MPR in
40
41 43 patients with hypertension, the 0–19% MPR group had a 1.5-fold risk of medical
42
43 44 complications relative to the 80–100% MPR group.

44
45
46 47 **Conclusions:** In patients with hypertension, high continuity of care and medication adherence
47
48 48 for the first 2 years of diagnosis can help prevent medical complications and promote
49
50 49 patients' health. Therefore, effective strategies to improve continuity of care and medication
51
52 50 adherence are required. Future research should include some factors that may affect the
53
54 51 incidence of hypertensive complications, such as familial aggregation, and hazard
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56 52 stratification by the level of blood pressure, which were not considered in this study.
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3 51 Therefore, there may be residual confounding and still room for improvement.
4

5 52 **Keywords:** ambulatory care-sensitive conditions, continuity of care, hypertension,
6
7 medication adherence, retrospective cohort
8
9

10 54

11
12 55 **Strengths and limitations of this study**
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- 14
15 56 • The study had a long follow-up period (18 years) and included over 100,000 participants,
16
17 57 which are regarded as indicators of relatively higher reliability and validity in cohort
18
19 58 studies according to the European Society of Cardiology.
20
21 59 • The utilised database contained data on health service use of over 50,000,000 Korean
22
23 60 citizens' (99.7% of whole population), indicating that it was nationally representative.
24
25 61 • Hypertension (International Classification of Disease-11 code: I.10) was selected from
26
27 62 the Ambulatory Care-Sensitive Conditions list in the Agency of Health Research and
28
29 63 Quality standard and hypertensive complications were selected according to the
30
31 64 definitions from World Health Organization and the advice from specialists in internal
32
33 65 medicine.
34
35 66 • Owing to the retrospective nature of the study, the possibility of bias, including
36
37 67 misclassification bias, may not be excluded.
38
39 68 • Some factors that may affect the incidence of hypertensive complications, such as
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41 69 familial aggregation, and hazard stratification by the level of blood pressure were not
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43 70 considered.
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78 INTRODUCTION

79 Hypertension is one of the most important health issues worldwide (1). In terms of the
80 global prevalence of hypertension, almost 1.4 billion people, which is almost 20% of the
81 world population, have hypertension (2). In an evaluation of all risk factors by the World
82 Health Organization (WHO) and the Global Burden of Disease Study, hypertension ranked
83 first as a contributor to the burden of disease at 20%, with a contribution greater than that of
84 obesity (3). Hypertension progresses in approximately 50%, 33%, and 10–15% of cases
85 caused by coronary artery disease or heart disease, stroke, and renal disease, respectively (1).
86 It is closely related to ischemic heart disease, which is the leading cause of death worldwide
87 (4).

88 Hypertension is also classified as an Ambulatory Care-Sensitive Condition (ACSCs),
89 which means that early diagnosis and intervention are beneficial in preventing the medical
90 complications that may result in death, hospitalisation, and major medical costs (5). ACSCs
91 have been classified by the Agency of Health Research and Quality (AHRQ), and 16 diseases
92 selected by the AHRQ can be prevented from progressing if they are treated effectively in a
93 timely manner by providing prevention and medical services (6). By treating and managing
94 these conditions early, hospitalisation due to aggravation or complications of the disease can
95 be reduced (6). Early intervention in an outpatient setting slows the onset and progression of
96 the disease (7) and prevents avoidable hospitalisation (5,8).

97 ACSCs are representative indicators for evaluating the accessibility and quality of
98 primary care, which plays a pivotal role in 'early intervention' (9). To assess the
99 management of ACSCs in medical institutions, including primary care, COC and MPR are
100 the most important indicators of measurement tools. COC refers to a continuous relationship

1
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3 101 and consultation between a patient and physician, and the MPR refers to the compliance rate
4
5 102 of medications as prescribed by a physician. Therefore, these two measurements are broadly
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7
8 103 used for the evaluation of the ACSCs management.
9

10 104 Several studies have focused on hypertension, continuity of care, and medication
11
12 105 adherence (10-12). However, the study design of previous studies was limited by the setting,
13
14 106 and the small number of patients included (10-12). This study used the National Health
15
16 107 Insurance Service (NHIS) database, in which over 50 million patients are registered (13).
17
18 108 Patient data include physician visit information and the prescription data for each visit (13).
19
20 109 As national health insurance is mandatory for every citizen in South Korea, the reliability of
21
22 110 the data is high, and data are representative of the population on a national level (13).
23
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26 111 The objective of this study was to analyse the effect of providing timely and effective
27
28 112 ambulatory care to patients with early hypertension on preventing the occurrence of medical
29
30 113 complications using COC and the MPR as indicators of effective care. The secondary
31
32 114 objective was to assess the outcomes of hypertension according to the level of hospital at
33
34 115 which patients were treated.
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40 117 **METHODS**

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42 118 This national, population-based, retrospective cohort study investigated the incidence of
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44 119 hypertension from 1 January 2002 to 31 December 2019 among the general population in
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46 120 South Korea. We analysed the secondary data using national insurance claims data at all levels of
47
48 121 hospitals in South Korea. Unlike previous studies on the risk of complications according to the
49
50 122 continuity of care and medication adherence, this study examined the time variance, including
51
52 123 the time from the first visit to initial 2 years of the medical institution, and limited the
53
54 124 patient's age (>30 years) (14).
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126 **Inclusion and exclusion of participants**

127 This study used the data of 1.4 million individuals from the NHIS database from 2002 to
128 2019 selected using stratified sampling (13). The NHIS database, which includes the medical
129 records of more than 50 million people, is stratified by sex and age group (18 strata) (13). To
130 maintain representativeness, sampling was performed according to the demographic
131 characteristics and income deciles in South Korea (13). In addition, these cohort data were
132 linked to the national health check-up database, including data of over 66% of the general
133 population (over 33 million) in South Korea. Furthermore, information on the cause of death
134 was provided by linkage to death data from the National Statistical Office (15-16).

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

141 To avoid bias, we excluded patients who were prescribed drugs less than twice
142 (n=53,662) to enable proper measurement of the MPR; patients aged <30 years (n=6,630) to
143 exclude low-risk patients; patients who visited medical institutions in 2002 and 2003
144 (n=54,180) as a washout period; patients with medical complications (n=5,698) to prevent
145 contamination of results on the incidence of complications; those who were diagnosed with
146 hypertension from 2016–2019 (n=38,340) to maintain the baseline characteristics of the
147 target population; patients who had taken related drugs or undergone related procedures or
148 surgeries according to the AHRQ guidelines on ACSCs (n=2,047); those who had visited the
149 medical institution before the index date due to hypertension (n=9,919), or who visited the
150 emergency room or were hospitalised within 2 years of the index date according to the AHRQ

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2
3 151 guidelines on ACSCs research (n=8,907) to avoid unequal baseline characteristics; those who
4
5 152 died within 2 years of the index date (n=1,065) for the washout period of mortality and
6
7 153 severity; and patients who visited medical institutions less than four times after the index date
8
9 154 (n=22,308) to enable proper measurement of COC. After these exclusions, retrospective data
10
11 155 of 102,519 patients (out of 1.4 million members of the general population of South Korea)
12
13 156 were included in the analysis (Figure 1).
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18 19 158 **Measurements**

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21 159 Continuity of care was defined as ‘continuance of care by a healthcare provider to meet a
22
23 160 patient's medical needs providing high quality and harmonised care’ (17). Additionally, with
24
25 161 a good level of continuous care provided by the physicians, the hospitalisation rate,
26
27 162 prevalence, and the number of medical visits are reduced (18). Methods for measuring
28
29 163 continuity of care include the COC, Usual Provider of Care index, Most Frequent Primary
30
31 164 Care, and the Modified Continuity Index (19). We utilised COC as an indicator.
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35 165 Shortell identified four core factors required for COC (20). First, the data should be of
36
37 166 individuals. Second, analysed data should be distinguished and compared when individuals
38
39 167 visit different medical institutions and providers. Third, COC should reflect the total number
40
41 168 of visits for care. Finally, appropriate referral patterns should also be considered (21). South
42
43 169 Korea has a fee-for-service system without a proper referral system (21).
44
45
46

47 170 COC measures continuity of care on a scale of 0 to 1, based on all visits to medical
48
49 171 institutions. It weighs both the frequency of visits to each provider and the dispersion of visits
50
51 172 between providers. If every visit for medical services to one provider, the COC index will be
52
53 173 1. The formula is:

$$54
55
56
57 174 \text{COC} = \frac{\sum_{j=1}^M n_j^2 - N}{N(N-1)}$$

1
2
3 175 N=total number of ambulatory care
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6 176 n_j =number of visits to provider
7

8
9 177 M=total number of provider
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12 178
13

14 179 The major drawback of this method is that it is not applicable if there are fewer than four
15 visits (22). This is not an ultimate threshold of COC, but is used in practice.
16

17 180 Medication adherence refers to the degree of compliance with medications prescribed by
18 a physician. Accurate tracking of prescription data is essential for analysing medication
19 adherence as well as effectively predicting healthcare costs and utilisation (22). To measure
20 medication adherence, the MPR and proportion of days covered are usually used for analysis
21 (12). The formula for MPR is:
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30 186
$$MPR = \frac{\text{Sum of days' supply for all fills in a period}}{\text{\# of days in period}}$$

31
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36 188 The MPR is usually estimated using prescription data. For example, prescription data
37 were provided with the defined daily dose. A MPR value of 100% means complete
38 medication adherence.
39
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41

42 191 The major limitation of MPR estimation is that it is based on retrospective data review,
43 and patients may have received unrecorded medication. However, owing to the Korean
44 pharmaceutical information system, unrecorded prescriptions cannot occur in NHIS data (12).
45
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47
48
49 194 Another limitation of the MPR method is sharing medicine between family members.
50
51
52 195 However, sharing of medication is likely to be minimal, because each medical appointment is
53 scheduled according to the number of days of medication prescribed in South Korea. The
54 major strength of the MPR method is that by researching diseases containing data on
55
56
57 197 changeable parameters, such as blood pressure, HbA1c, fasting blood glucose, researchers
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3 199 can closely estimate patient health status based on the drugs that they are prescribed. We
4
5 200 received professional advice from specialists in internal medicine and cardiology for the
6
7 201 selection of antihypertensive drugs and its list (Supplementary Table 1).
8
9

10 202 Medical complications of hypertension—coronary artery disease, vascular complications,
11
12 203 cerebrovascular disease, heart disease, and hypertensive nephropathy—were selected based
13
14 204 on WHO documentation (1). The WHO documentation also includes cognitive impairment as
15
16 205 a type of hypertensive complication (1), but as data on mental examination were unavailable,
17
18 206 we were unable to include cognitive impairment as a complication in our study.
19
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24 208 **Statistical analysis**

25
26 209 Explanatory variables influencing COC, MPR, and the occurrence of complications in
27
28 210 patients with hypertension included sex, age, insurance type, income, outpatient status, COC,
29
30 211 MPR level of the patient, number of visits, number of providers, main medical institution, and
31
32 212 comorbidities. Patients without values for any of these variables were excluded. Subgroup
33
34 213 analysis was performed for primary care visits to assess the efficiency of the healthcare
35
36 214 system in South Korea. The statistical significance of differences between the groups was
37
38 215 assessed using Student's t-test and analysis of variance. P-values <0.05 were regarded as
39
40 216 statistically significant. The Kruskal–Wallis test and Wilcoxon rank-sum test were used to
41
42 217 compare continuous variables that were not normally distributed, and Fisher's exact test was
43
44 218 used to compare categorical variables between the groups.
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49 219 Insurance type is divided into two categories: health insurance beneficiaries and medical
50
51 220 aid recipients. The national health insurance system in South Korea enables medical aid
52
53 221 recipients to obtain free health services because it is based on the lowest level of household
54
55 222 income. Income was divided into 10 categories as described in Supplementary Table 2.
56
57

58 223 COC was divided into two categories: high (COC index=1) and low (COC index <1).
59
60

1
2
3 224 Most COC-related research in South Korea uses this standard because the overall levels of
4
5 225 COC in South Korea are high compared with those in other countries. According to
6
7 226 Organization for Economic Cooperation and Development (OECD) statistics on healthcare
8
9 227 utilisation, South Korea has a three-fold higher outpatient and inpatient medical care use than
10
11 228 the OECD average (23). In this study, the mean COC index was 0.8112, confirming the high
12
13 229 level of COC in South Korea. In previous studies, the MPR has generally been divided into
14
15 230 three categories (>80%, 50–80%, and <50% of MPR) or two categories (>60% and <60% of
16
17 231 MPR) (24, 25). However, we decided to use five categories (excellent: 80–100%, good: 60–
18
19 232 80%, normal: 40–60%, bad: 20–40%, and very bad: 0–20%) to enable more detailed analysis
20
21 233 of the MPR. Outpatient status, number of visits, number of providers, and main medical
22
23 234 institution are required factors for calculating the COC level.

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28 235 The term ‘comorbidity’ indicates that patients or participants have different diseases that
29
30 236 can affect the results of the study. Comorbidities are sometimes confused with complications,
31
32 237 but comorbidities differ from complications because they do not occur as a result of the target
33
34 238 disease. Defining comorbidities plays a pivotal role in risk adjustment because confounding
35
36 239 can occur if the results are not adjusted for comorbidities.

37
38
39
40 240 In this study, we selected diabetes and dyslipidaemia as comorbidities, which are co-
41
42 241 factors of cardiovascular disease, cerebrovascular disease, and hypertensive nephropathy (26-
43
44 242 28). These two types of disease could affect the incidence of hypertensive complications.

45
46
47 243 Categorical variables associated with the level of COC (low vs high), were compared
48
49 244 using the chi-square test. A comparison of complications according to the COC and MPR was
50
51 245 performed using Kaplan–Meier survival curves and log-rank tests. The differences in medical
52
53 246 complications according to COC and MPR were examined. The Cox proportional hazards
54
55 247 model was used to compare the risk. Hazard ratios (HRs) and 95% confidence intervals (CIs)
56
57 248 were estimated using multivariable Cox proportional hazards regression.

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3 249
45 **Ethical issues**
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7
8 251 Ethics approval for the study was obtained from the Institutional Review Board at Korea
9
10 252 University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required
11
12 253 owing to the retrospective nature of the study. The study has been prepared in accordance
13
14 254 with the STROBE guidelines. This study was conducted in accordance with the Declaration
15
16
17 255 of Helsinki.

18
19 256
2021 **Patient and public involvement**
22

23
24 258 We did not involve patients and public in this study because it was a retrospective study
25
26 259 using data from the NHIS database.

27
28 260
2930 **RESULTS**
31

32
33 262 The average COC level in the hypertension group was 0.8112. The average MPR in the
34
35 263 hypertension group was 73.3%.

36
37 264
3839 **General characteristics of patients with hypertension**
40

41
42 266 The patient characteristics are shown in Supplementary Table 1. Of the patients, 51,522
43
44 267 (50.3%) were male and 50,997 (49.7%) were female. The over 80year age group was the
45
46 268 largest age group (27.0%), followed by the 70–79 year (21.5%) and 60–69-year (18.1%) age
47
48 269 groups. The vast majority of patients (94.0%) were covered by national health insurance. The
49
50 270 largest income categories were the 9th–10th decile (27.0%), followed by the 7th–8th decile
51
52 271 (21.5%) and the 5th–6th decile (18.1%). The most common outpatient visit categories were
53
54 272 7–9 visits (29.7%), followed by 10–12 visits (29.5%), and ≥ 13 visits (25.0%). Of the patients,
55
56 273 50.9% visited only one provider and 31.0% visited two providers. The majority of patients
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274 visited clinics (70.8%). The most common comorbidities were dyslipidaemia (49.8%) and
 275 diabetes (28.7%). Approximately half the patients (50.9%) had a high level of COC. The
 276 majority of patients (55.5%) had an excellent MPR. The most frequent years of diagnosis
 277 were 2004 (10.1%), 2005 (12.1%), and 2006 (10.1%).

278

279 **Risk of complications of hypertension according to the COC and MPR level**

280 Compared with the high COC group, participants in the low COC group had a
 281 significantly higher risk of complications (HR: 1.14, 95% CI: 1.10–1.17) (Table 1).

282

283 **Table 1. Risk of complications of hypertension according to the COC level**

COC level	No. of patients	No. of events	IR per 1,000 PYR	HR ^a (95% CI)	<i>p</i>
High	52,179	7,143	15.4	Ref	
Low	50,340	8,142	17.7	1.14 (1.10–1.17)***	<0.001

284 CI, confidence interval; COC, continuity of care; HR, hazard ratio; IR, incidence rate; PYR,
 285 person-years at risk

286 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of
 287 hospital, and Comorbidities

288 ***, *p*<0.001

289

290 Compared with the excellent MPR group, the risk of developing hypertensive
 291 complications was significantly higher in the good, normal, bad, and very bad MPR groups
 292 (Table 2).

293

294 **Table 2. Risk of hypertensive complications according to the MPR level**

MPR level	No. of patients	No. of events	IR per 1,000 PYR	HR ^a (95% CI)	<i>p</i>
Excellent	56,939	7,143	14.1	Ref	
Good	16,012	2,695	17.9	1.24 (1.18–1.29)***	<0.001
Normal	11,808	2,146	19.5	1.36 (1.29–1.42)***	<0.001
Bad	9,996	1,834	20.3	1.42 (1.35–1.50)***	<0.001
Very bad	7,764	1,467	21.4	1.50 (1.42–1.59)***	<0.001

295 HR, hazard ratio; IR, incidence rate; MPR, medication possession ratio; PYR, person-years at
 296 risk

297 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level
 298 of hospital, and Comorbidities

299 ***, *p*<0.001

301 **Risk of specific types of hypertension complication according to the COC and MPR** 302 **levels**

303 Kaplan–Meier survival curves showing the time until complications occurred according to
 304 the COC and MPR are shown in Supplementary Figures 1 and 2, respectively. The risks of
 305 developing coronary artery disease, vascular complications, cerebrovascular disease, heart
 306 disease, and hypertensive nephropathy according to each COC and MPR level are shown in
 307 Tables 3 and 4, respectively. Patients with diabetes and high cholesterol had a higher
 308 incidence of hypertensive complications than patients without diabetes and high cholesterol,
 309 respectively.

310

311 **Table 3. Risk of medical complications of hypertension according to the COC level**

Complication	Parameter	COC level	
		High	Low
CAD	Events (N)	2,117	2,350
	IR per 1,000 PYR	4.4	4.9
	HR ^a (95% CI)	Ref	1.10 (1.03–1.16)**
	<i>p</i>	-	0.002
Vascular complications	Events (N)	412	451
	IR per 1,000 PYR	0.8	0.9
	HR ^a (95% CI)	Ref	1.07 (0.94–1.23)
	<i>p</i>	-	0.302
Cerebrovascular disease	Events (N)	3,639	4,178
	IR per 1,000 PYR	7.6	8.7
	HR ^a (95% CI)	Ref	1.14 (1.09–1.19)***
	<i>p</i>	-	<0.001
Heart disease	Events (N)	2,602	2,951
	IR per 1,000 PYR	5.4	6.1
	HR ^a (95% CI)	Ref	1.11 (1.06–1.17)***
	<i>p</i>	-	<0.001
Hypertensive nephropathy	Events (N)	716	768
	IR per 1,000 PYR	1.5	1.6
	HR ^a (95% CI)	Ref	1.05 (0.95–1.16)
	<i>p</i>	-	0.367

312 CAD, coronary artery disease; CI, confidence interval; COC, continuity of care; HR, hazard

313 ratio; IR, incidence rate; N, Number; PYR, person-years at risk

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3 314 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level
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5 315 of hospital, and Comorbidities
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8 316 **, $p < .01$ ***, $p < 0.001$
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317 **Table 4. Risk of medical complications of hypertension according to the MPR level**

Complication	Parameter	MPR level				
		Excellent	Good	Normal	Bad	Very bad
CAD	Events (N)	2,081	811	635	535	405
	IR per 1,000 PYR	4	5.1	5.5	5.6	5.5
	HR ^a (95% CI)	Ref	1.26 (1.16–1.37)***	1.35 (1.23–1.47)***	1.38 (1.26–1.52)***	1.38 (1.24–1.53)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001
Vascular complications	Events (N)	393	154	120	107	89
	IR per 1,000 PYR	0.7	1	1	1.1	1.2
	HR ^a (95% CI)	Ref	1.25 (1.04–1.51)*	1.33 (1.08–1.63)**	1.45 (1.17–1.79)***	1.59 (1.26–2.00)***
	<i>p</i>	-	0.018	0.007	0.001	<0.001
Cerebrovascular disease	Events (N)	3,613	1,312	1,120	997	775
	IR per 1,000 PYR	6.9	8.4	9.8	10.6	10.8

Complication	Parameter	MPR level				
		Excellent	Good	Normal	Bad	Very bad
	HR ^a (95% CI)	Ref	1.18 (1.11– 1.26)***	1.38 (1.29– 1.47)***	1.51 (1.41– 1.62)***	1.54 (1.43– 1.67)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001
Heart disease	Events (N)	2,585	981	788	659	540
	IR per 1,000 PYR	4.9	6.2	6.8	6.9	7.4
	HR ^a (95% CI)	Ref	1.21 (1.13– 1.30)***	1.33 (1.23– 1.44)***	1.36 (1.25– 1.48)***	1.47 (1.34– 1.62)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001
Hypertensive nephropathy	Events (N)	633	278	232	194	147
	IR per 1,000 PYR	1.2	1.7	2	2	2
	HR ^a (95% CI)	Ref	1.39 (1.21– 1.60)***	1.58 (1.36– 1.84)***	1.62 (1.38– 1.90)***	1.62 (1.35– 1.94)***
	<i>p</i>	-	<0.001	<0.001	<0.001	<0.001

318 CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MPR, medication possession ratio; N, Number; PYR, person-years at
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320 ^a Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and Comorbidities

321 *, $p < .05$; **, $p < .01$ ***, $p < 0.001$

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3 322 The risk of coronary artery disease was significantly higher in the low than in the high COC
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5 323 group (HR: 1.10, 95% CI: 1.03–1.16) (Table 3). Compared with the excellent MPR group, the
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8 324 risk of coronary artery disease was significantly higher in the good, normal, bad, and very bad
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10 325 MPR groups (Table 4).

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12 326 The risk of vascular complications did not differ significantly according to the COC level
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14 327 (Table 3). Compared with the excellent MPR group, the risk of vascular complications was
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17 328 significantly higher in the good, normal, bad, and very bad MPR groups (Table 4).

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19 329 The risk of cerebrovascular disease was significantly higher in the low continuity group
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21 330 than the high COC group (HR: 1.14, 95% CI: 1.09–1.19) (Table 3). Compared with the
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24 331 excellent MPR group, the risk of cerebrovascular disease was significantly higher in the good,
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26 332 normal, bad, and very bad MPR groups (Table 4).

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28 333 The risk of heart disease was significantly higher in the low COC than in the high COC
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30 334 group (HR: 1.11, 95% CI: 1.06–1.17) (Table 3). Compared with the excellent MPR group, the
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33 335 risk of heart disease was significantly higher in the good, normal, bad, and very bad MPR
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35 336 groups (Table 4).

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37 337 The risk of hypertensive nephropathy did not differ significantly according to the COC
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39 338 level (Table 3). Compared with the excellent MPR group, the risk of hypertensive nephropathy
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42 339 was significantly higher in the good, normal, bad, and very bad MPR groups (Table 4).
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46 47 341 **Subgroup analysis of risk of medical complications according to the COC and MPR** 48 49 342 **levels in primary care clinics**

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51 343 A subgroup analysis of the risk of medical complications according to the COC level and
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53 344 MPR in patients with hypertension attending primary care clinics showed that the risk of
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56 345 developing complications was significantly higher in the low than in the high COC group
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58 346 (HR: 1.16, 95% CI: 1.12–1.21). Compared with the excellent MPR group, the risk of
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3 347 developing hypertensive complications was significantly higher in the good, normal, bad, and
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5 348 very bad MPR groups. Compared with patients who had 4–6 visits, the risk of developing
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7 349 medical complications was significantly lower in patients with 7–9, 10–12, or ≥ 13 visits
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10 350 (Supplementary Table 3).

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12 352 **DISCUSSION**

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17 353 In this study, we analysed the differences in hypertensive complications according to
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19 354 continuity of care and medication adherence in patients with hypertension. The study
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21 355 highlights the fact that COC and MPR were associated with the occurrence of complications
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23 356 caused by hypertension. Overall, for patients with hypertension in the low as compared to the
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25 357 high COC group, the risk of complications was significantly higher. In this study, the order of
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27 358 establishing health policies related to COC, MPR can increase the response and lower the risk
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29 359 of long-term complications within the first 2 years of diagnosis of hypertension. Similarly,
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31 360 the risk of developing coronary artery disease, cerebrovascular disease, and heart disease was
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33 361 greater in the low as compared to the high COC group. Regarding overall medication
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35 362 adherence, in comparison to the excellent MPR group (80–100%), the good (60–79%),
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37 363 normal (40–59%), bad (20–39%), and very bad groups (0–19%) were at significantly higher
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39 364 risk of developing hypertensive complications, such as coronary artery disease, vascular
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41 365 complications, cerebrovascular disease, heart disease, and hypertensive nephropathy.

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46 366 Other COC and MPR studies have found that patients with low medication adherence are
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48 367 more likely to result in progress to inpatient or mortality (HR: 1.24, 95% CI: 1.18–1.29). The
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50 368 differences were attributed to the type of antihypertensive medication, follow-up period, and
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52 369 the differences in the definition of medication adherence. We overcame these limitations
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54 370 because of the 18-year follow-up period.

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57 371 Another MPR study showed that low medication adherence is more likely to result in

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3 372 progress to inpatient or mortality (HR: 1.57, 95% CI: 1.40–1.76). This result is similar to that
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5 373 of our study (29).

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8 374 Other COC and MPR studies focused on hypertension and diabetes, and found that for
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10 375 hypertension, low COC medication adherence is more likely to result in progress to death in
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12 376 hospitalised patients (HR: 1.66, 95% CI: 1.55–1.77; HR: 1.14, 95% CI: 1.08–1.20,
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14 377 respectively). Low COC and medication adherence are more likely to result in progress to
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16 378 hospitalisation or death among outpatients (HR: 1.67, 95% CI: 1.47–1.90). The differences
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18 379 were attributed to the fact that the incidence of hypertensive complications was not among
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20 380 their outcomes, and the reason for hospitalisation varied, potentially causing the
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22 381 overestimation of the results.

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25 382 This study had several strengths. First, the study obtained population representativeness
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27 383 because we utilised NHIS data and the subscription of national health insurance is legally
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29 384 mandatory (covering approximately 99.7%) in South Korea. Second, the disease was selected
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31 385 from AHRQ standards of ACSCs and hypertensive complications were selected according to
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33 386 the definitions from WHO (1). Third, there is a standard in ACSCs related to hypertension (no
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35 387 cardiac procedures included), which is often omitted in previous studies, and this is the first
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37 388 attempt at a long-term (18-year) analysis of ACSCs (hypertension) with a clearer definition of
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39 389 patients and its incidence rate of complications.

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42 390 However, this study also had several limitations. First, as only the continuity of care and
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44 391 medication adherence in the initial 2 years were measured, follow-up after 2 years was not
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46 392 reflected in the effects of changes in care. Second, the risk of complications or blood pressure
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48 393 level was not analysed in this study. Third, whether other underlying diseases or external
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50 394 factors may affect the results, such as familial aggregation, the levels of blood pressure, and
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52 395 over-prescription of drugs, of this study could not be fully excluded. Fourth, owing to the
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54 396 retrospective nature of this observational study, misclassification or recall bias may impact the
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3 397 validity of this study. Finally, this study can be elevated to mortality or factor study. The
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5 398 case-control or prospective cohort study to elucidate the association between COC, MPR
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8 399 levels, and the mortality of patients with hypertensive complications with its characteristics.
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10 400 There are several policies for the management of ACSCs worldwide. For example, there
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12 401 are policies for diabetes, cervical cancer, and asthma in Australia and policies for depression,
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14 402 cancer, and asthma in the UK and USA; it is possible to provide primary care in a timely
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16 403 manner and manage chronic diseases more efficiently by including more diseases subject to
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18 404 chronic disease management in the ACSCs (30). Therefore, a follow-up study on the
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20 405 differences in the risk of complications according to changes in care should be conducted in
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22 406 the future.
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26 407 This study sheds light on the association between continuity of care and medication
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28 408 adherence and the incidence of hypertensive complications, such as coronary artery disease
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30 409 and heart disease. The continuous management of blood pressure can be beneficial to prevent
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32 410 hypertensive complications among patients with hypertension. The implication should be
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34 411 based on subgroup analysis (Supplementary file).; visiting primary care facilities is
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36 412 adequately beneficial to patients with hypertension. Therefore, the Korean government
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38 413 should establish health policies related to chronic diseases that need management with a view
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40 414 to long-term care. Moreover, because of its unique structure (lack of a gatekeeper system
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42 415 [referral system]), the healthcare system of South Korea is facing a financial shortage. Future
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44 416 studies should compare the cost-effectiveness of care provided by different types of medical
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46 417 institutions, such as general hospitals and clinics.
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52 419 **Authors' contributions**

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54 420 Conceptualisation: Dayea Kim, Methodology: Dayea Kim, Software: Dayea Kim, Data
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56 421 curation: Dayea Kim, Writing – Original draft preparation: Jaewoo Cha, Visualisation: Jaewoo
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3 422 Cha, Investigation: Dayea Kim, Jaewoo Cha, Supervision: Jaewoo Cha, Validation: Jaewoo

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5 423 Cha, Writing – Reviewing and editing: Dayea Kim, Jaewoo Cha

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10 425 **Competing interests**

11
12 426 None declared.

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16
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18
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21 430 not-for-profit sectors.

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26 432 **Data sharing statement**

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28 433 Raw data were generated by the National Health Insurance Service. Derived data supporting

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30 434 the findings of this study are available from the corresponding author, Jaewoo Cha, on request.

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35 436 **Ethics statements**

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37 437 Ethics approval for the study was obtained from the Institutional Review Board at Korea

38 438 University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required due

39 439 to the retrospective nature of the study.

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44 441 **Patient consent for publication**

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46 442 Not applicable.

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51 444 **Acknowledgements**

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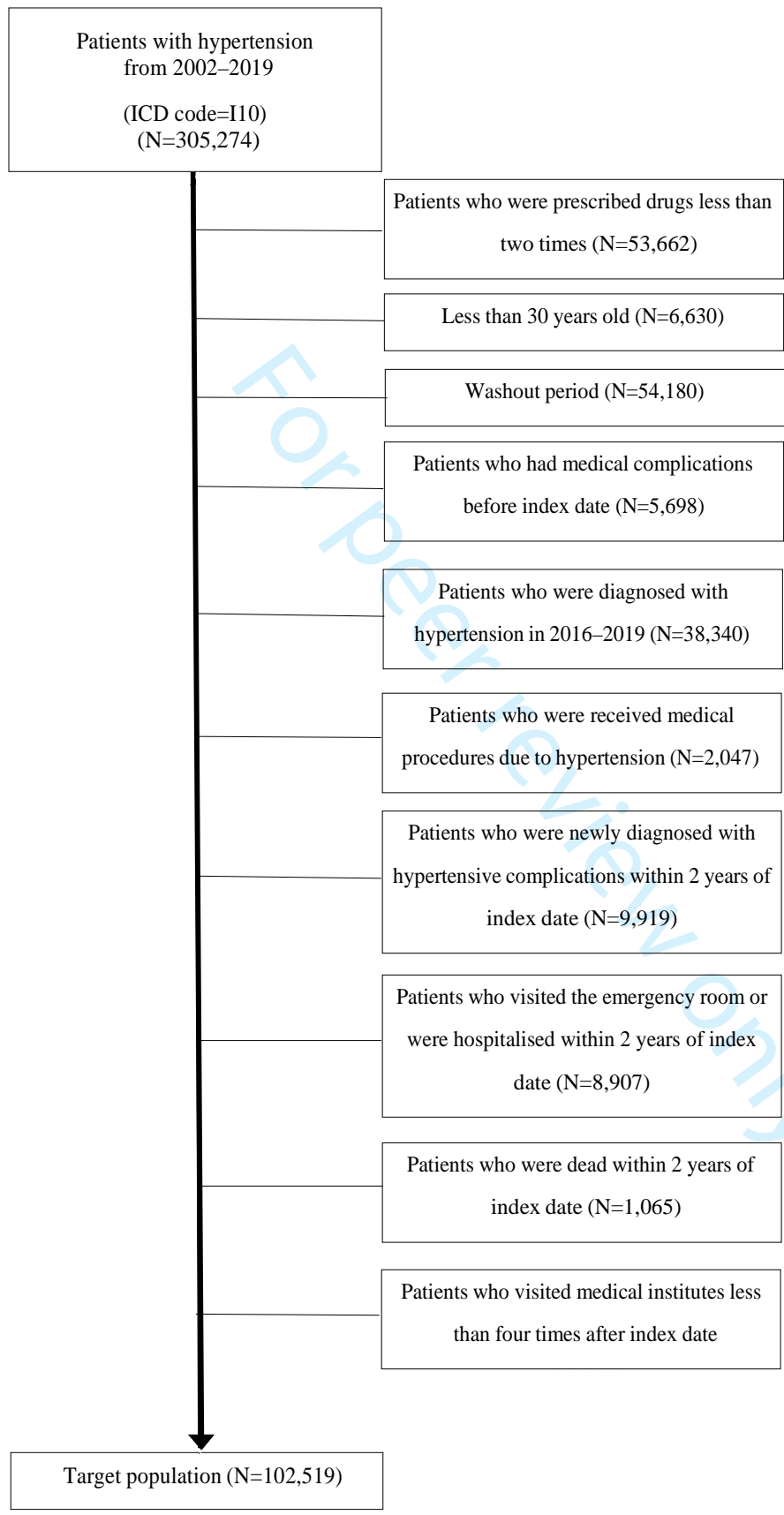
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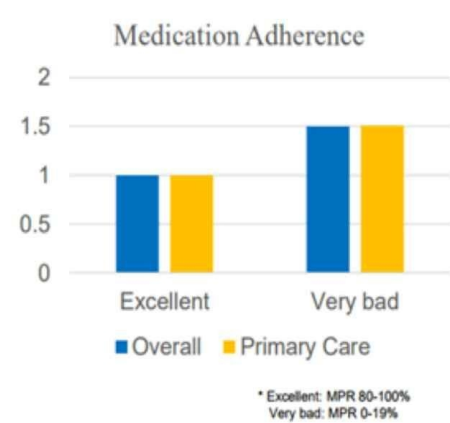
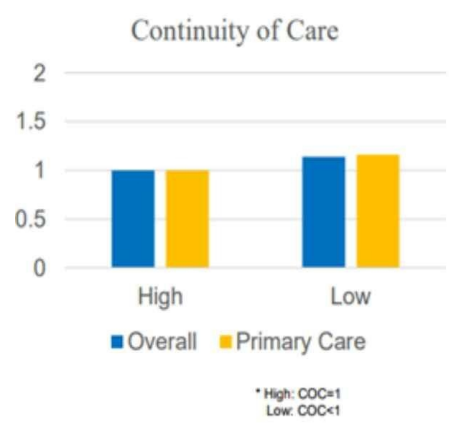
524 **Figure legend**

525 **Figure 1.** Flow diagram of the study population
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Supplementary Materials**Supplementary Table 1. Antihypertensive drugs included**

Drugs included
Captopril, enalapril, ramipril, candesartan, fimasartan, losartan, olmesartan, telmisartan, valsartan, carteolol, nadolol, propranolol, nifedipine, felodipine, amlodipine, lercanidipine, CCB, diltiazem, verapamil, atenolol, bisoprolol, celiprolol, metoprolol, amosulalol, carvedilol, bevantolol, doxazosin, terazosin, hydrochlorothiazide, indapamide, furosemide, torsemide, spironolactone, amiloride, hydralazine, minoxidil, and nitroprusside.

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Supplementary Table 2. General characteristics of the study population

Variable		N	%
Total		102,519	100.0
Sex	Male	51,522	50.3
	Female	50,997	49.7
Age	30–39	2,084	2.0
	40–49	16,943	16.5
	50–59	15,266	14.9
	60–69	18,532	18.1
	70–79	22,056	21.5
	>80	27,638	27.0
Insurance type	National Health Insurance	96,325	94.0
	Others	6,194	6.0
Income	0 decile (0 USD)	284	2.0
	1st and 2nd deciles (857–1,781 USD)	16,943	16.5
	3rd and 4th deciles (2,609–3,273 USD)	15,266	14.9
	5th and 6th deciles (3,963–4,620 USD)	18,532	18.1
	7th and 8th deciles (5,357–6,323 USD)	22,056	21.5
	9th and 10th deciles (7,925–11,288 USD)	27,638	27.0
Number of visits	4–6	16,175	15.8
	7–9	30,475	29.7
	10–12	30,236	29.5
	≥13	25,633	25.0
Number of providers	1	52,197	50.9
	2	31,825	31.0
	3	12,462	12.2
	≥4	6,053	5.9

Variable		N	%
Level of hospital	Tertiary general hospital	4,857	4.7
	General hospital	9,292	9.1
	Hospital	6,270	6.1
	Clinic	72,612	70.8
	Others	9,488	9.3
Comorbidity: Diabetes	Yes	29,391	28.7
	No	73,128	71.3
Comorbidity: Dyslipidaemia	Yes	51,048	49.8
	No	51,471	50.2
COC	High (COC index=1)	52,179	50.9
	Low (COC index <1)	50,340	49.1
MPR	Excellent (80–100%)	56,939	55.5
	Good (60–79%)	16,012	15.6
	Normal (40–59%)	11,808	11.5
	Bad (20–39%)	9,996	9.8
	Very bad (0–19%)	7,764	7.6
Year of diagnosis	2004	10,357	10.1
	2005	12,362	12.1
	2006	10,321	10.1
	2007	9,017	8.8
	2008	9,101	8.9
	2009	8,906	8.7
	2010	8,082	7.9
	2011	7,807	7.6
	2012	7,623	7.4
	2013	6,699	6.5
	2014	5,772	5.6
	2015	6,472	6.3

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COC, continuity of care; N, number; MPR, medication possession ratio

For peer review only

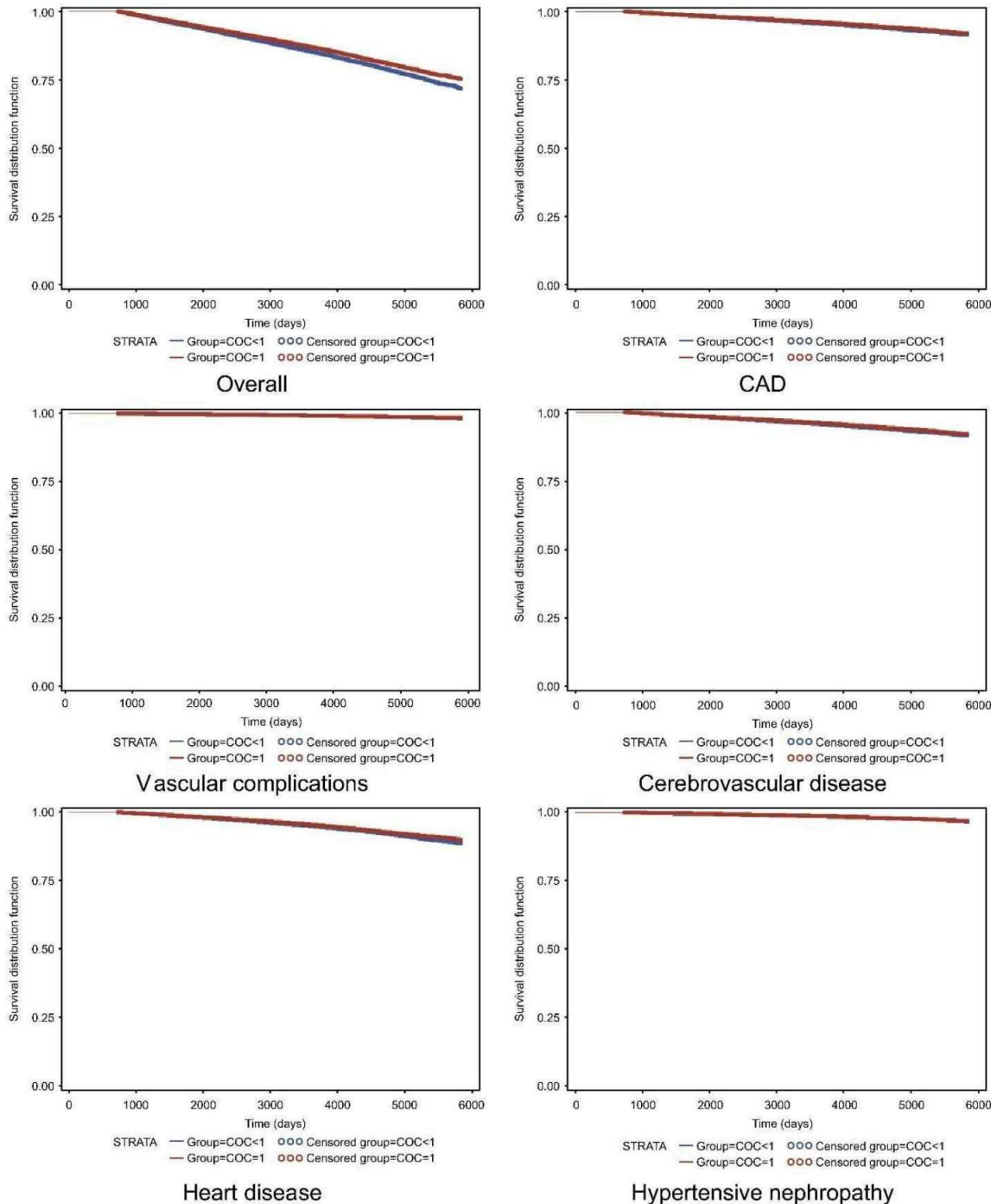
Supplementary Table 3. Subgroup analysis of the hazard ratio of medical complications according to the COC and MPR levels in clinics (primary care)

	Hazard Ratio				
	Patients	Events (N)	IR per 1000PYR	HR (95% CI)	<i>p</i> -value
COC level					
High	36,273	4,437	13.8	Ref	
Low	36,339	5,405	16.2	1.16 (1.12–1.21)***	<0.001
MPR Level					
Excellent	41,414	4,674	12.8	Ref	
Good	11,326	1,738	16.1	1.21 (1.15–1.28)***	<0.001
Normal	7,953	1,362	18.1	1.37 (1.29–1.45)***	<0.001
Bad	6,518	1,118	18.7	1.43 (1.34–1.52)***	<0.001
Very bad	5,401	950	19.6	1.51 (1.40–1.61)***	<0.001
Number of visits					
4–6 times	8,770	1,388	17.8	Ref	
7–9 times	18,484	2,490	15.1	0.86 (0.80–0.91)***	<0.001
10–12 times	23,493	3,112	14.1	0.78 (0.73–0.83)***	<0.001
Over 13 times	21,865	2,852	14.9	0.85 (0.80–0.91)***	<0.001

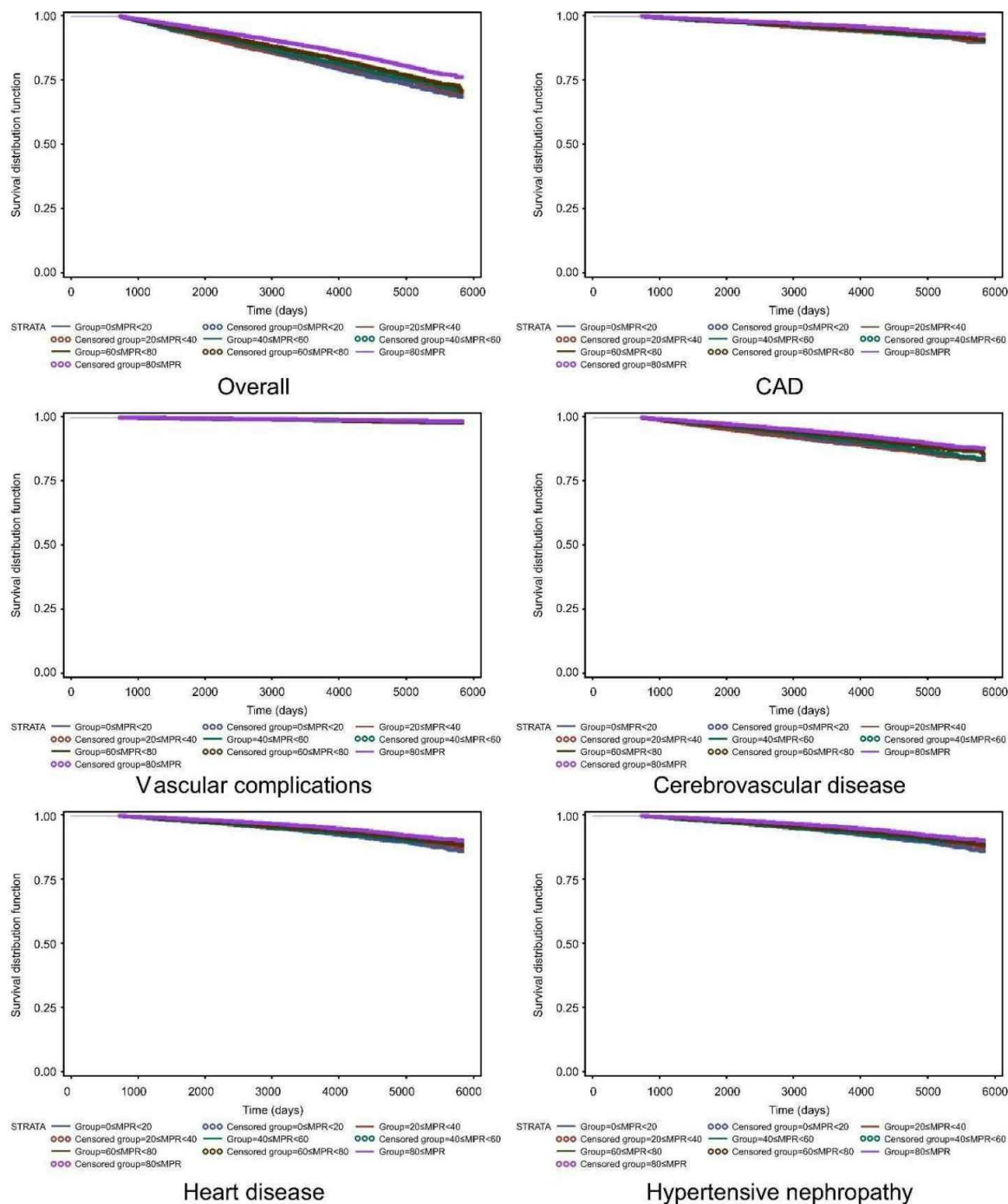
CI, confidence interval; COC, continuity of care; ; HR, hazards ratio; IR, Incidence rate; MPR, medication possession

ratio; N, number; PYR, person years at risk

***Significance at $p < 0.001$.



Supplementary Figure 1. Kaplan–Meier Curve of medical complications according to the Continuity of Care (COC) level



Supplementary Figure 2. Kaplan–Meier Curve of medical complications according to the medicine possession ratio (MPR) level

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4–5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6–10
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7–10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5–9
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6–9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9–10
		(b) Describe any methods used to examine subgroups and interactions	9–10
		(c) Explain how missing data were addressed	6
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6–7
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11–13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	11–18
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11–19
		(b) Report category boundaries when continuous variables were categorized	11–19
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11–19
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	19–20
Discussion			
Key results	18	Summarise key results with reference to study objectives	20–21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21–22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20–22
Generalisability	21	Discuss the generalisability (external validity) of the study results	20–22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.