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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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Conflict of interest

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

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 have a 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.

Keywords: Continuity of care, medication adherence, ambulatory care-sensitive conditions, hypertension, retrospective cohort

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

include not only physician visit information but also the prescription data for each visit (13). Since the National Health Insurance is mandatory for every citizen in Korea, the reliability of the data is extremely high, and data on the national level of population is stored in big data centres (NHIS, 2022).

The objective of this study was to analyse the effect of ACSCs provided in a timely and effective manner and prevent the occurrence of medical complications by treating and managing early cases of hypertension that have already occurred using continuity of care (COC) and medication possession ratio (MPR) measurements. Additionally, it aims to analyse the primary care of ACSCs in different levels of hospitals and their outcomes.

METHODS

Inclusion and exclusion of participants

This study is a national population-based retrospective cohort study and investigated the incidence of hypertension from 2002.01.01 to 2019.12.31 among the general population in Korea. Unlike previous studies on the risk of complications according to COC and medication adherence in the first 2 years, the present study examined the time variance, including the time of the first visit to the medical institution and patient age (more than 30 years).14-16 Patients who were prescribed drugs less than two times due to proper measurement of MPR (Number of excluded participants=53,662), were aged <30 years for the extraction of higher risk population (Number of excluded participants= 6,630), who visited medical institutes in 2002 and 2003 (wash-out period, number of excluded participants=54,180), who had medical complications before the index date due to the prevention of contamination of results on the incidence (Number of excluded participants=5,698), who were diagnosed with hypertension from 2016–2019 for maintaining the baseline characteristics of target population (Number of excluded participants=38,340),

who had taken related drugs or undergone related procedures or surgeries due to the suggestions from AHRQ on ACSCs research (Number of excluded participants=2,047), who had visited the medical institution before the index date due to hypertension to avoid unequal baseline characteristics of patients (Number of excluded participants=9,919), who visited the emergency room or were hospitalized within 2 years of the index date based on the suggestions from AHRQ on ACSCs research (Number of excluded participants=8,907), who died within 2 years of the index date for the washout period of mortality and severity (Number of excluded participants=1,065), and who visited the medical institute less than four times after the index date due to a proper measurement of COC (Number of excluded participants=22,308) were excluded to avoid bias such as misclassification bias or contamination of the results. Finally, 102,519 participants were included in the study from the retrospective data of 1 million members of the general population of Korea [Supplementary Figure 1].

Measurements

COC is defined as 'continuance of care by a healthcare provider to meet a patient's medical needs providing high quality and harmonised care (17). Additionally, with a good level of continuous care with doctors, the hospitalisation rate, prevalence rate, and the number of examinations are reduced (18). Methods for measuring COC include Usual Provider Care (UPC), most frequent primary care (MFPC), and modified modified continuity index (MMCI) (19).

Medication adherence refers to the degree of compliance with medications prescribed by a doctor (20). Accurate tracking of prescription data is essential for analysing medication adherence as well as effectively predicting healthcare costs and utilisation (20).

To measure medication adherence, the medication possession ratio (MPR) and proportion of

days covered (PDC) are usually used for analysis (21). We used COC for continuity of care and MPR to estimate medication adherence using NHI data, which tracks prescription data completely (12). We received professional advice from doctors of internal medicine or cardiology for the antihypertensive drug selection [Supplementary Table 1].

Data sources

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

Variables and Statistics

Factors influencing COC in patients with hypertension and the occurrence of complications included the sex, age, insurance type, income, outpatient status, COC of the patient, depending on the number of visits, number of providers, main medical institution, and comorbidities. Missing values for any valuables were initially eliminated. There was no lost to follow up because the dataset was based on medical record system and analyzed retrospectively. Subgroup analysis was performed for primary care because of efficiency of health system in Korea. Statistical significance was tested for mean and standard deviation using Student's t-test and analysis of variance. A p-value of <0.05 was regarded to be

statistically significant, and if the assumption was not satisfied, Kruskal, a non-parametric test method, was utilized. In addition, the Wallis test, Wilcoxon rank-sum test, and Fisher's exact test were used.

Depending on the level of COC (COC index low vs. high), observations and differences in results according to independent variables were applied using the chi-squared test.

A comparison of complications according to COC and MPR was performed using Kaplan–Meier survival curves and log-rank tests. The differences in medical complications according to continuity of care and medication adherence were examined. The applied Cox proportional hazards model for incidence was analyzed. The output value of the Cox proportional hazards model is presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Ethics approval for the study was obtained from the Institutional Review Board at Korea University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required due to the retrospective nature of the study. The study has been prepared in accordance with the STROBE guidelines.

Patient and Public Involvement

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

RESULTS

General characteristics of patients with hypertension

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

In terms of sex, 51,522 (50.3%) patients were men, and 50,997 (49.7%) were women.

In terms of age, we categorized age groups for age stratification. Participants aged 50-59 years accounted for the largest share at 30.7%, followed by those aged 60–69 years (24.5%), 40–49 years (20.7%), 70–79 years (15.1%), 30–39 years (5.2%), 80 years or older (3.8%).

Regarding the type of insurance, NHI insurers accounted for the majority (94.0%) followed by other insurance at 6.0%.

The income level was divided into ten sections, which follow the official Korean standard of household income. 9th–10th decile (27.0%), 7th–8th decile (21.5%), 5th–6th decile (18.1%), 1–2 decile (16.5%), over three deciles was followed by the 4th decile (14.9%), and the 0th decile (2.0%).

As for the number of outpatient visits for treatment, 7–9 times were the most frequent at 29.7%, followed by 10–12 times (29.5%), 13 times or more (25.0%), and finally 4–6 times (15.8%).

As for the number of providers visited, it includes changes in medical institutes and doctors. 50.9% of the patients visited only one hospital (provider) followed by two places (provider) such as outpatient clinics (31.0%), three places (provider) (12.2%), and four places

(provider) or more (5.9%).

Clinics accounted for 70.8% of major medical institutions, followed by others (9.3%), general hospitals (9.1%), hospitals (6.1%), and tertiary general hospitals (4.7%).

With respect to comorbidities, there were more cases of diabetes in the group without diabetes

(71.3%) than in the group with diabetes (28.7%). Dyslipidemia was also higher in the group without Dyslipidaemia was also higher in the group without dyslipidemia (50.2%) than in that with dyslipidemia (49.8%). The level of COC is divided into a high- level group (COC=1) and a low–level group (COC<1). CoC level accounted for 50.9% of high-level group, followed by low-level group (49.1%).

MPR was divided into five categories (Excellent=80-100%, Good=60-79%, Normal=40-59%,

Bad=20-39%, and Very bad=0-19%). The number of patients with excellent MPR was 55.5%, the highest, followed by good (15.6%), normal (11.5%), bad (9.8%), and very bad (7.6%). The year of diagnosis was also added from 2004 to 2015 [Table 1]. Finally, in terms of year of diagnosis, it accounted for in 2004 (10.1%), 2005 (12.1%), 2006 (10.1%), 2007 (8.8%), 2008 (8.9%), 2009 (8.7%), 2010 (7.9%), 2011 (7.6%), 2012 (7.4%), 2013 (6.5%), 2014 (5.6%), 2015 (6.4%) [Table 1].

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)	*p-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)	*p-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:1.29z-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)** **
	p-value	-	**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)

	p-value	-	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)** ***
	p-value	-	**<.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)** ***
	p-value	-	**<.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)
	p-value	-	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) *****
	p-value	-	**<.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) *****
	p-value	-	**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) *****
	p-value	-	**<.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) *****
	p-value	-	**<.001**	**<.001**	**<.001**	**<.001**

Hypertensive nephropathy	Events(N)	633	278	232	194	147
	IR per 1000PYR	1.2	1.7	2	2	2
	[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)** ***
	p-value	-	**<.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.

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

In patients with hypertension in the low-adherence group (COC<1) compared to the high-adherence group (COC=1) the risk of developing medical complications was 1.16 times higher (HR=1.16, 95% CI:1.12–1.21) and this difference 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%) were 1.21 (HR=1.21, 95% 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 1.51 times (HR=1.51, 95% CI:1.40–1.61) at higher risk of medical complications, respectively and all were statistically significant.

When it comes to the number of visits, 4-6 times compared to 7-9 times, 10-12 times, and over 13 times of the risk of developing medical complications was 0.86 times (HR=0.86, 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% CI:0.80–0.91) higher and this difference were statistically significant [Supplementary Table 2].

DISCUSSION

This study highlights the fact that the continuity of care and the order of establishing health policies can increase response and lower the risk of long-term complications within the first two years of diagnosis of hypertension.

In the present study, COC and medication adherence were associated with the occurrence of complications caused by hypertension. Overall, for patients 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 and statistically significant. Similarly, with regards to coronary sinus, cerebrovascular disease, and coronary heart disease, the risk of

developing pulse disease, cerebrovascular disease, and coronary disease, respectively was greater in the low continuity group than in the high continuity of care group.

In terms of overall medication adherence, in comparison to the excellent medication adherence group (80–100%), the good group (60–79%) was 1.24, 1.26, 1.25, 1.18, 1.21, and 1.39 times, normal group (40–59%) 1.36, 1.35, 1.33, 1.38, 1.33, and 1.58 times, bad group (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, 1.59, 1.13, 1.47, and 1.62 times at higher risk of hypertensive complications, coronary artery disease, vascular complications, cerebrovascular disease, heart disease, and hypertensive nephropathy, respectively, and all were statistically significant.

This study had several strengths. First, the study obtained population representativeness because national health insurance is mandatory in Korea. Second, medical complications were selected according to the AHRQ standards. Third, this is the first attempt at a long-term (17-year) analysis of ACSCs with medical complications.

However, this study also had several limitations. First, since only the continuity of treatment and medication adherence in the initial 2 years were measured, follow-up after 2 years was not reflected in the effects of changes in care. Second, the risk of complications or blood pressure level was not analysed in this study. Third, whether other underlying diseases or external factors may affect the results of this study could not be fully excluded. Fourth, due the retrospective nature of this observational study, recall bias may impact the validity of this study.

There are several policies for the management of ACSCs around the world. For example, policies for diabetes, cervical cancer, and asthma in Australia and policies for depression, cancer, and asthma in the UK and USA; it is possible to provide primary care in a timely manner and manage chronic diseases more efficiently by including more diseases subject to chronic disease management in the ACSCs.

A follow-up study on the differences in the risk of complications according to changes in care should be conducted in the future.

Transparency statement

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

SUMMARY BOXES

What is already known on this topic:

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

What this study adds:

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

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.

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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)

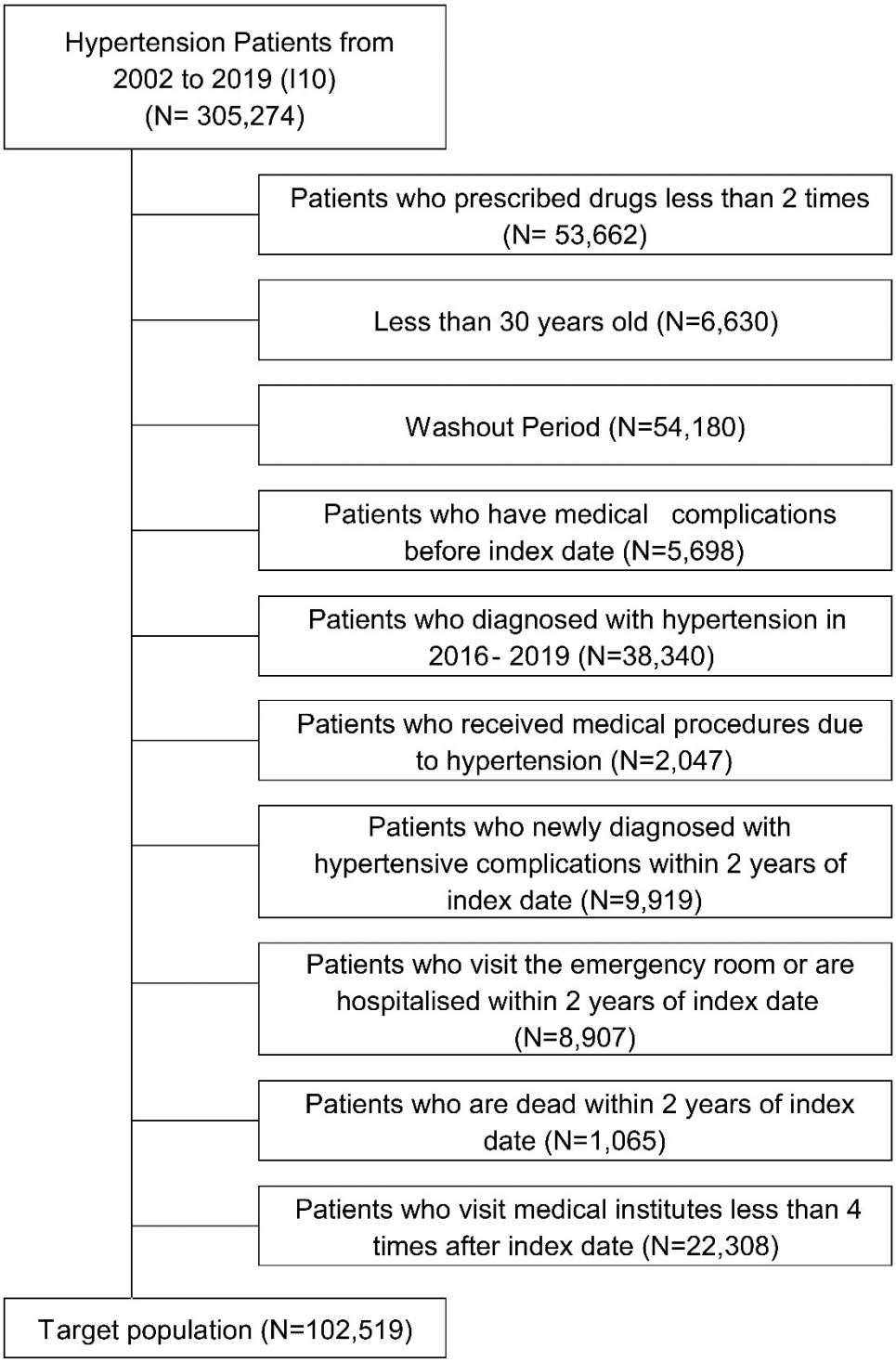
	Hazard Ratio				
	Patients	Events(N)	IR per 1000PYR	HR (95% CI)	*p-value*
COC level					
High	36,273	4,437	13.8	Ref	
Low	36,339	5,405	16.2	**1.16(1.12-1.21)*** **	**<.001**
MPR Level					
Excellent	41,414	4,674	12.8	Ref	
Good	11,326	1,738	16.1	**1.21(1.15-1.28)*** **	**<.001**
Normal	7,953	1,362	18.1	**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**

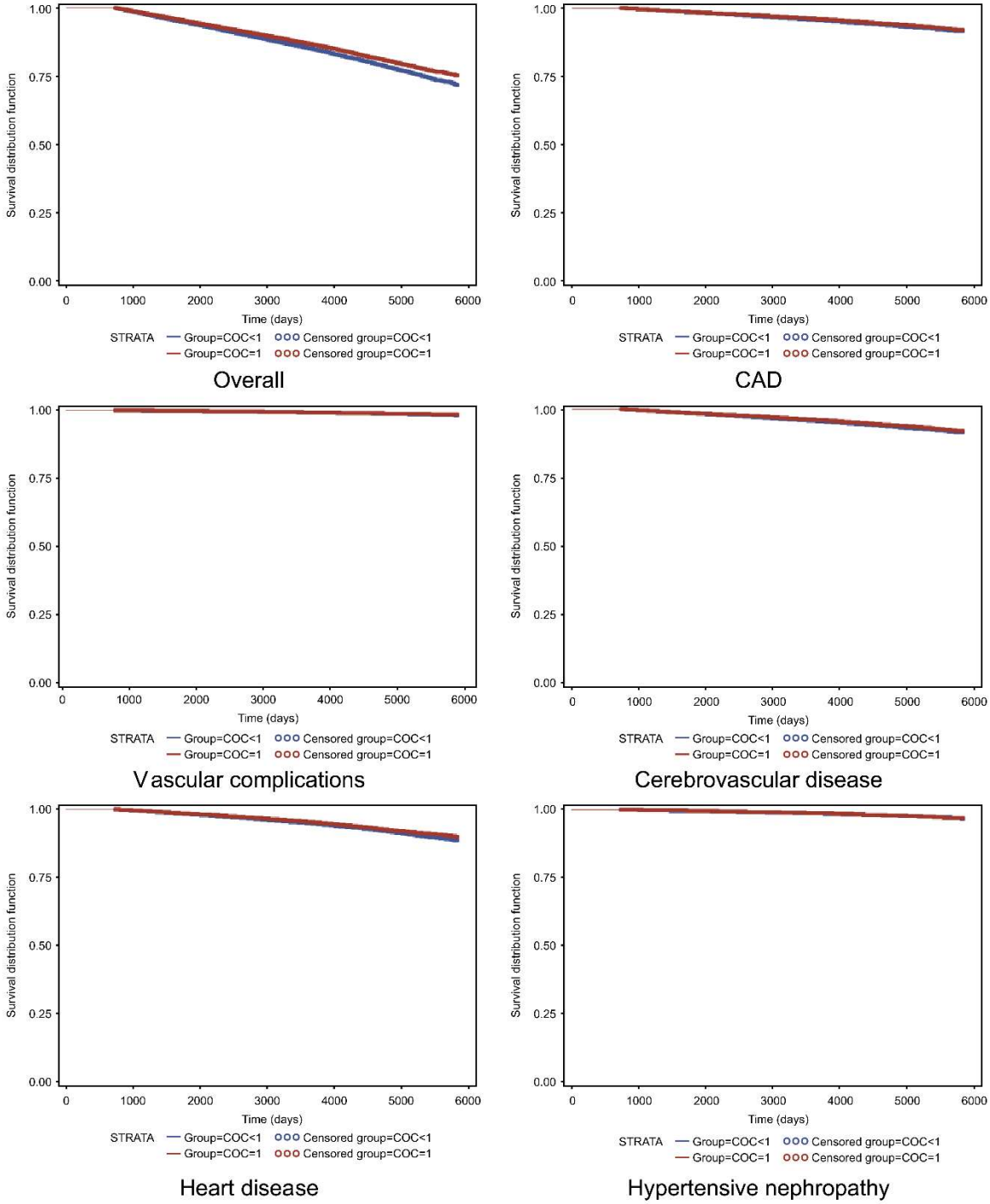
N, Number; COC, continuity of care; MPR, Medication Possession Ratio; HR, hazards ratio; CI, confidence interval; IR, Incidence rate; PYR, Person Years at Risk

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

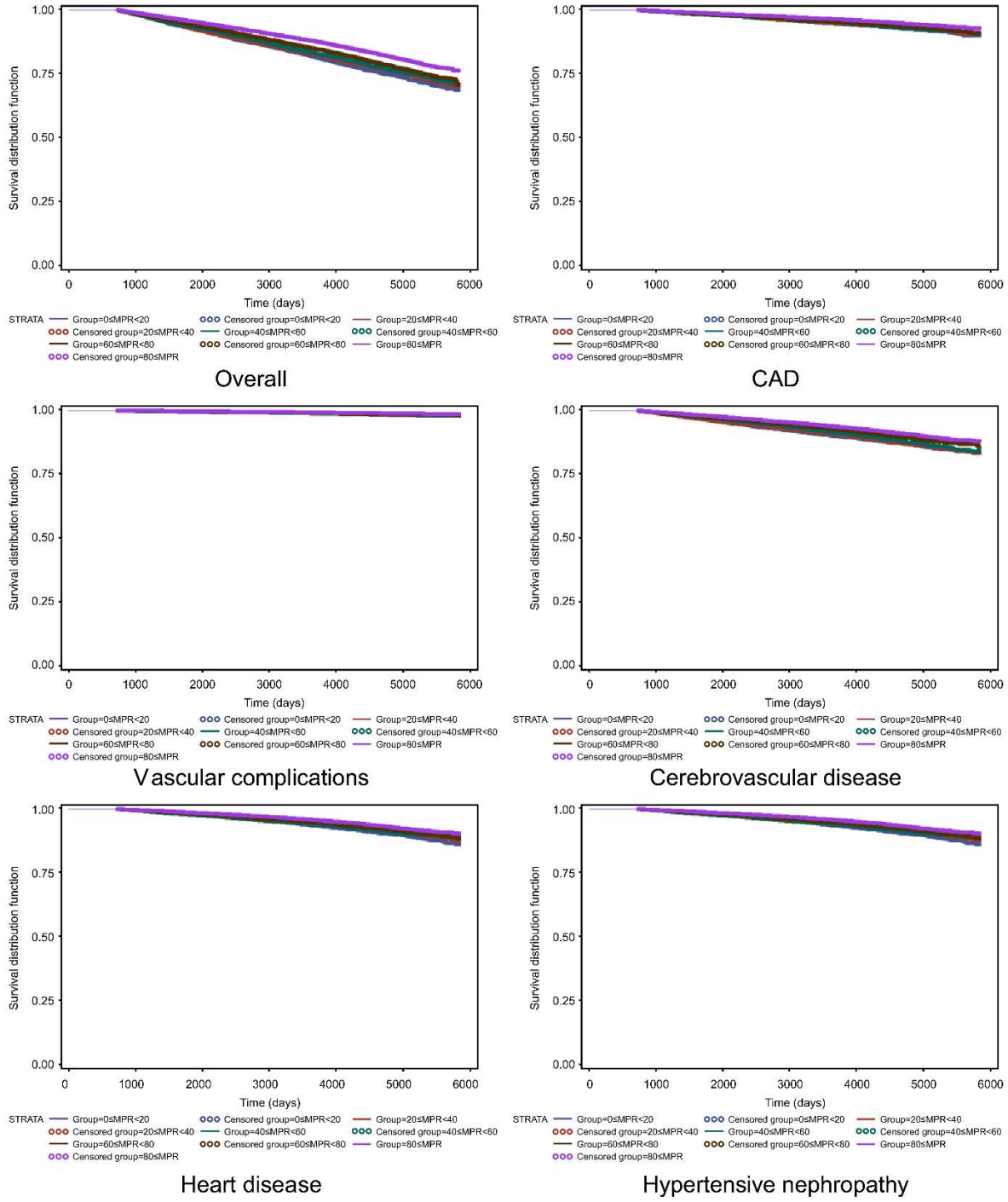
Supplementary Figure 1. Flow diagram of study population



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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-22
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—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.

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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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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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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: Medical claims data at all levels of hospitals in Korea.

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

Main outcome measures: The levels of continuity of care 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 a level of continuity of care (COC) to measure continuity of care and medication possession ratio (MPR) to measure medication adherence.

Results: The average level of COC in the hypertension group was 0.8112. The average proportion of MPR in the hypertension group was 73.3%. Continuity of care in patients with hypertension showed varying results: the low COC group had a 1.14-fold increased risk of medical complications compared to the high COC group. In terms of a level of medication adherence in patients with hypertension, the 0–19% MPR group had a 1.5-fold risk of medical complications relative to the 80–100% MPR group.

Conclusions: In patients with hypertension, high continuity of care and medication adherence for the first 2 years of diagnosis can help prevent medical complications and promote patients' health. Therefore, effective strategies to improve continuity of care and medication adherence are required. Future research should include some factors that may affect the incidence of hypertensive complications such as familial aggregation, and hazard stratification by the level of blood pressure were not considered, so there may be residual confounding and still room for improvement.

Keywords: Continuity of care, medication adherence, ambulatory care-sensitive conditions, hypertension, retrospective cohort

Strengths and limitations of this study

- The study had a long follow-up period (18 years) and included over 100,000 participants, which are regarded as indicators of relatively higher reliability and validity in cohort studies according to the European Society of Cardiology.
- The database we utilsed contained data on health service use of over 50,000,000 Korean citizens' (99.7% of whole population), which means nationally representative.
- Hypertension (ICD-11 code=I.10) was selected from the ACSCs list in the Agency of Health Research and Quality standard and hypertensive complications were selected according to the World Health Organization and the advice from specialists in internal medicine.
- Due to the retrospective nature of the study, the possibility of bias, including misclassification bias, may not be excluded.
- Some factors that may affect the incidence of hypertensive complications such as familial aggregation, and hazard stratification by the level of blood pressure were not considered.

INTRODUCTION

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

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

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

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

The objective of this study was to analyse the effect of providing timely and effective ambulatory care to patients with early hypertension on preventing the occurrence of medical complications using COC and the medication possession ratio (MPR) as indicators of effective care. A secondary objective was to assess the outcomes of hypertension according to the level of hospital at which patients were treated.

METHODS

This national, population-based, retrospective cohort study investigated the incidence of hypertension from 1 January 2002 to 31 December 2019 among the general population in Korea. Unlike previous studies on the risk of complications according to the COC and medication adherence in the first 2 years, this study examined the time variance, including the time of the first visit to the medical institution and the patient's age (greater than 30 years) (14-15).

Inclusion and exclusion of participants

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

provided by linkage to death data from the National Statistical Office (16-17).

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

To avoid bias, we excluded patients who were prescribed drugs less than twice (n=53,662) to enable proper measurement of the MPR; patients aged <30 years (n=6,630) to exclude low-risk patients; patients who visited medical institutions in 2002 and 2003 (n=54,180) as a washout period; patients with medical complications (n=5,698) to prevent contamination of results on the incidence of complications; patients who were diagnosed with hypertension from 2016–2019 (n=38,340) to maintain the baseline characteristics of the target population; patients who had taken related drugs or undergone related procedures or surgeries according to the AHRQ guidelines on ambulatory care-sensitive conditions (n=2,047); patients who had visited the medical institution before the index date due to hypertension (n=9,919), or who visited the emergency room or were hospitalised within 2 years of the index date according to the AHRQ guidelines on ambulatory care-sensitive conditions (n=8,907) to avoid unequal baseline characteristics; patients who died within 2 years of the index date (n=1,065) for the washout period of mortality and severity; and patients who visited medical institutions less than four times after the index date (n=22,308) to enable proper measurement of COC. After these exclusions, retrospective data of 102,519 patients (out of 1 million members of the general population of Korea) were included in the analysis (Figure 1).

Measurements

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

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

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

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

N = total number of ambulatory care

n_j = number of visits to provider

M = total number of provider

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

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

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

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

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

Medication adherence refers to the degree of compliance with medications prescribed by a doctor (24). Accurate tracking of prescription data is essential for analysing medication adherence as well as effectively predicting healthcare costs and utilisation (23). To measure medication adherence, the MPR and proportion of days covered are usually used for analysis (12). We used the COC index and MPR to estimate medication adherence using NHI data, which tracks all prescription data (12). We received professional advice from specialists in internal medicine and cardiology for the selection of antihypertensive drugs (Supplementary table 1).

Medical complications of hypertension—coronary artery disease, vascular complications, cerebrovascular disease, heart disease, and hypertensive nephropathy—were selected based on WHO documentation (1). The WHO documentation also includes cognitive impairment as

a type of hypertensive complication (1), but as data on mental examination was unavailable, we were unable to include cognitive impairment as a complication in our study.

Statistical analysis

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

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

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

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

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

Outpatient status, number of visits, number of providers, main medical institution are required factors for calculating the COC level. We used the Charlson Comorbidity Index to measure comorbidities (28).

Categorical variables associated with the level of COC (low vs high), were compared using the chi-square test. A comparison of complications according to the COC and MPR was performed using Kaplan–Meier survival curves and log-rank tests. The differences in medical complications according to COC and medication adherence were examined. The Cox proportional hazards model was used to compare the risk. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards regression.

Ethical issues

Ethics approval for the study was obtained from the Institutional Review Board at Korea University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required due to the retrospective nature of the study. The study has been prepared in accordance with the STROBE guidelines.

Patient and public involvement

We did not involve patients and public in this study because it was a retrospective study using data from the NHIS database.

RESULTS

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

General characteristics of patients with hypertension

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

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

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

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)	*p*
High	52,179	7,143	15.4	Ref	
Low	50,340	8,142	17.7	**1.14 (1.10–1.17)*** **	**<0.001**

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

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

***,<0.001

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

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)	*p*
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**

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

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

***,<0.001

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

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

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

Table 3. Risk of medical complications of hypertension according to the continuity of 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)****
	p	-	**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)
	p	-	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)*****
	p	-	**<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)*****
	p	-	**<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)
	p	-	0.367

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

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

,<.01 *,<0.001

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)*** **
	p	-	**<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)*** **
	p	-	**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)*** **
	p	-	**<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)*** **
	p	-	**<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)*** **
	p	-	**<0.001**	**<0.001**	**<0.001**	**<0.001**

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

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

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

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

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

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

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

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

Subgroup analysis of risk of medical complications according to continuity of care and medication possession ratio levels in primary care clinics

A subgroup analysis of the risk of medical complications according to the COC level and MPR in patients with hypertension attending primary care clinics showed that the risk of developing complications was significantly higher in in the the low COC group than the high COC group (HR: 1.16, 95% CI: 1.12–1.21). Compared with the excellent MPR group, the

risk of developing hypertensive complications was significantly higher in the good, normal, bad, and very bad MPR groups. Compared with patients who had 4–6 visits, the risk of developing medical complications was significantly lower in patients with 7–9 visits, 10–12 visits, or 13 visits or more (Supplementary table 3).

DISCUSSION

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

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

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

of our study (29).

Other COC and MPR studies focused on hypertension and diabetes, and found that for hypertension, low medication adherence and low COC are more likely to result in progress to death in hospitalised patients (HR: 1.66 (95% CI:1.55-1.77) 1.14(95% CI: 1.08-1.20), respectively). Low medication adherence and low COC are more likely to result in progress to hospitalisation or death among outpatients (HR, 1.67(95% CI:1.47-1.90)). The differences were because the incidence of hypertensive complications were not among their outcomes, and the reason for hospitalisation varied, potentially causing the overestimation of the results.

This study had several strengths. First, the study obtained population representativeness because we utilised NHI data and NHI subscription is legally mandatory (covering approximately 99.7%) in Korea. Second, the disease was selected from AHRQ standards of ACSCs and hypertensive complications were selected according to the WHO. Third, there is a standard in ACSCs related to hypertension (no cardiac procedures included), which is often omitted in previous studies, and this is the first attempt at a long-term (18-year) analysis of ambulatory care-sensitive conditions (hypertension) with a clearer definition of patients and its incidence rate of complications. However, this study also had several limitations. First, as only the continuity of treatment and medication adherence in the initial 2 years were measured, follow-up after 2 years was not reflected in the effects of changes in care. Second, the risk of complications or blood pressure level was not analysed in this study. Third, whether other underlying diseases or external factors may affect the results, such as familal aggregation, the levels of blood pressure, and over-prescription of drugs, of this study could not be fully excluded. Fourth, due to the retrospective nature of this observational study, misclassification or recall bias may impact the validity of this study. Finally, this study can be elevated to mortality or factor study. The case–control or prospective cohort study to elucidate the association between COC, MPR levels, and the mortality of patients with

hypertensive complications with its characteristics.

There are several policies for the management of ambulatory care-sensitive conditions worldwide. For example, there are policies for diabetes, cervical cancer, and asthma in Australia and policies for depression, cancer, and asthma in the UK and USA; it is possible to provide primary care in a timely manner and manage chronic diseases more efficiently by including more diseases subject to chronic disease management in the ambulatory care-sensitive conditions (30). A follow-up study on the differences in the risk of complications according to changes in care should be conducted in the future.

This study sheds light on the association between COC and medication adherence and the incidence of hypertensive complications such as coronary artery disease and heart disease. The continuous management of blood pressure can be beneficial to prevent hypertensive complications among the patients with hypertension. The implication should be based on subgroup analysis, visiting medical institutes of primary care is adequately beneficial to patients with hypertension. Therefore, the Korean government should establish health policies related to chronic diseases that need management with a view to long-term care. Moreover, because of its unique structure (lack of a gatekeeper system (referral system)), the healthcare system of the Republic of Korea is facing a financial shortage. Future studies should compare the cost-effectiveness of care provided by different types of medical institutions, such as general hospitals and clinics.

a. Contributorship statement

Conceptualisation: Dayea Kim, Methodology: Dayea Kim, Software: Dayea Kim, Data curation: Dayea Kim, Writing – Original draft preparation: Jaewoo Cha, Visualisation: Jaewoo Cha, Investigation: Dayea Kim, Jaewoo Cha, Supervision: Jaewoo Cha, Validation: Jaewoo Cha, Writing – Reviewing and editing: Dayea Kim, Jaewoo Cha

b. Competing interests

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

c. Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

d. Data sharing statement

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

e. Ethics statements

Patient consent for publication

Not applicable

f. Acknowledgements

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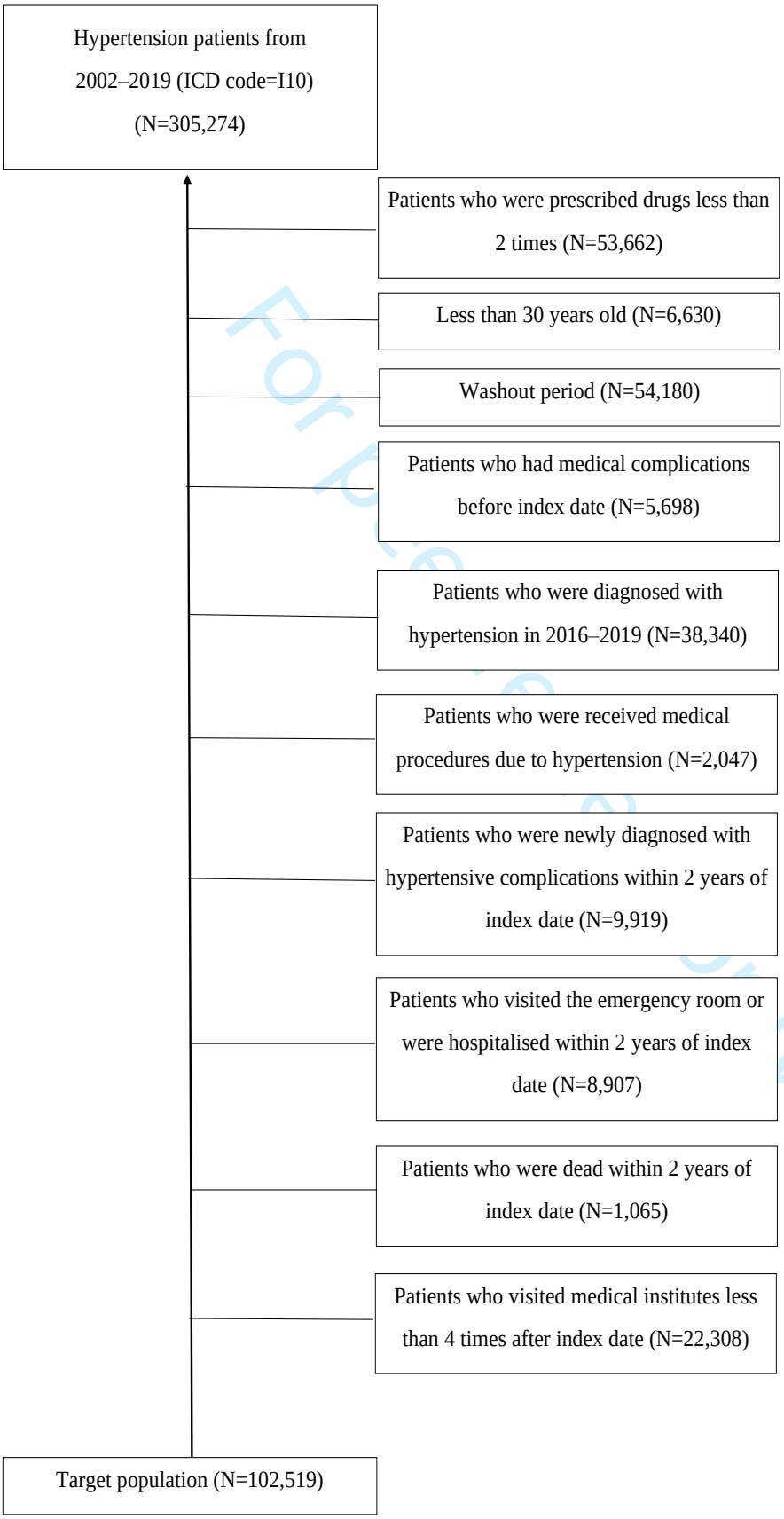
Figure 1. Flow diagram of the study population



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

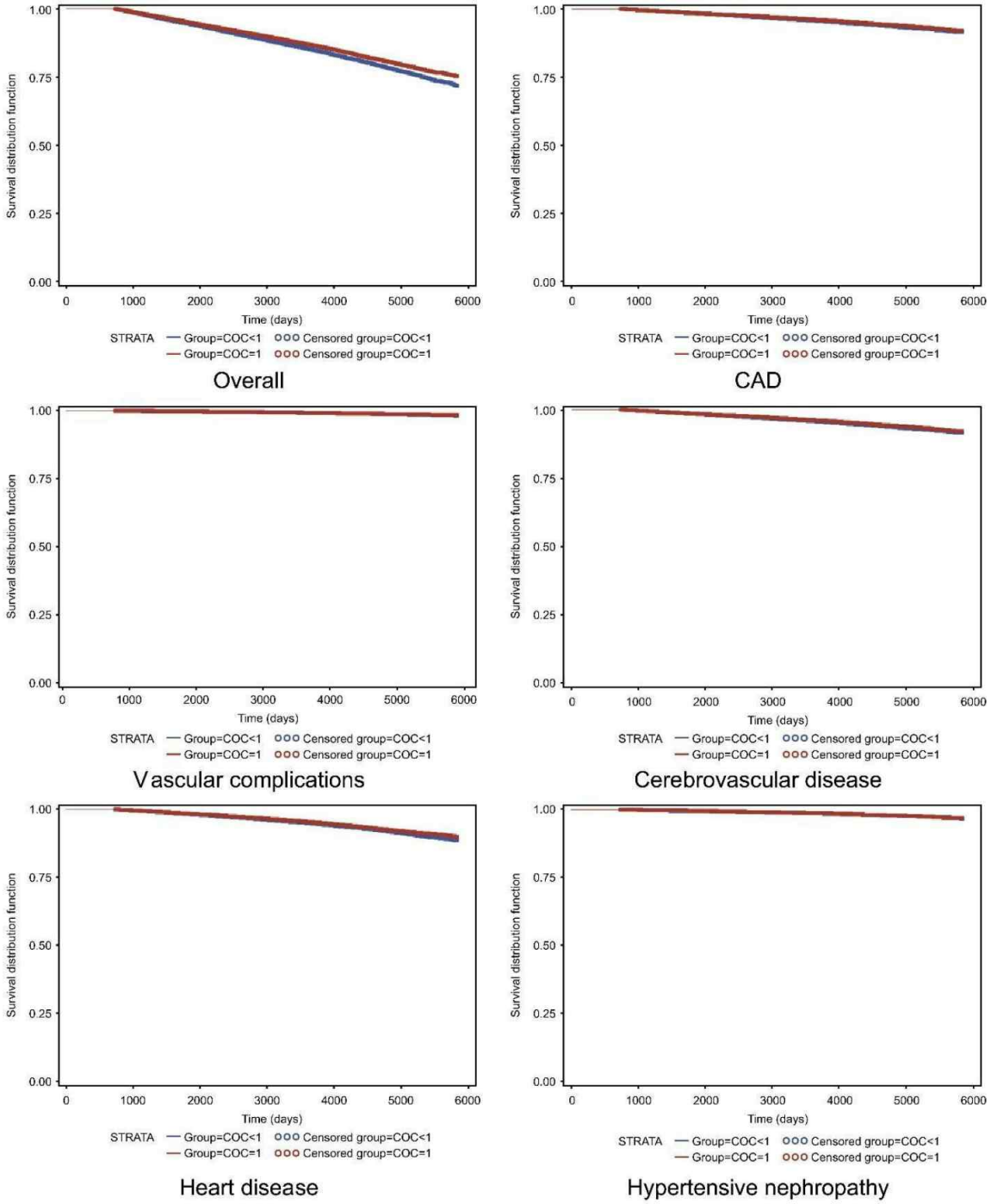
Supplementary Table 3. Subgroup analysis of the hazard ratio of medical complications according to COC and MPR levels in clinics (primary care)

	Hazard Ratio				
	Patients	Events (N)	IR per 1000PYR	HR (95% CI)	*p-value*
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**

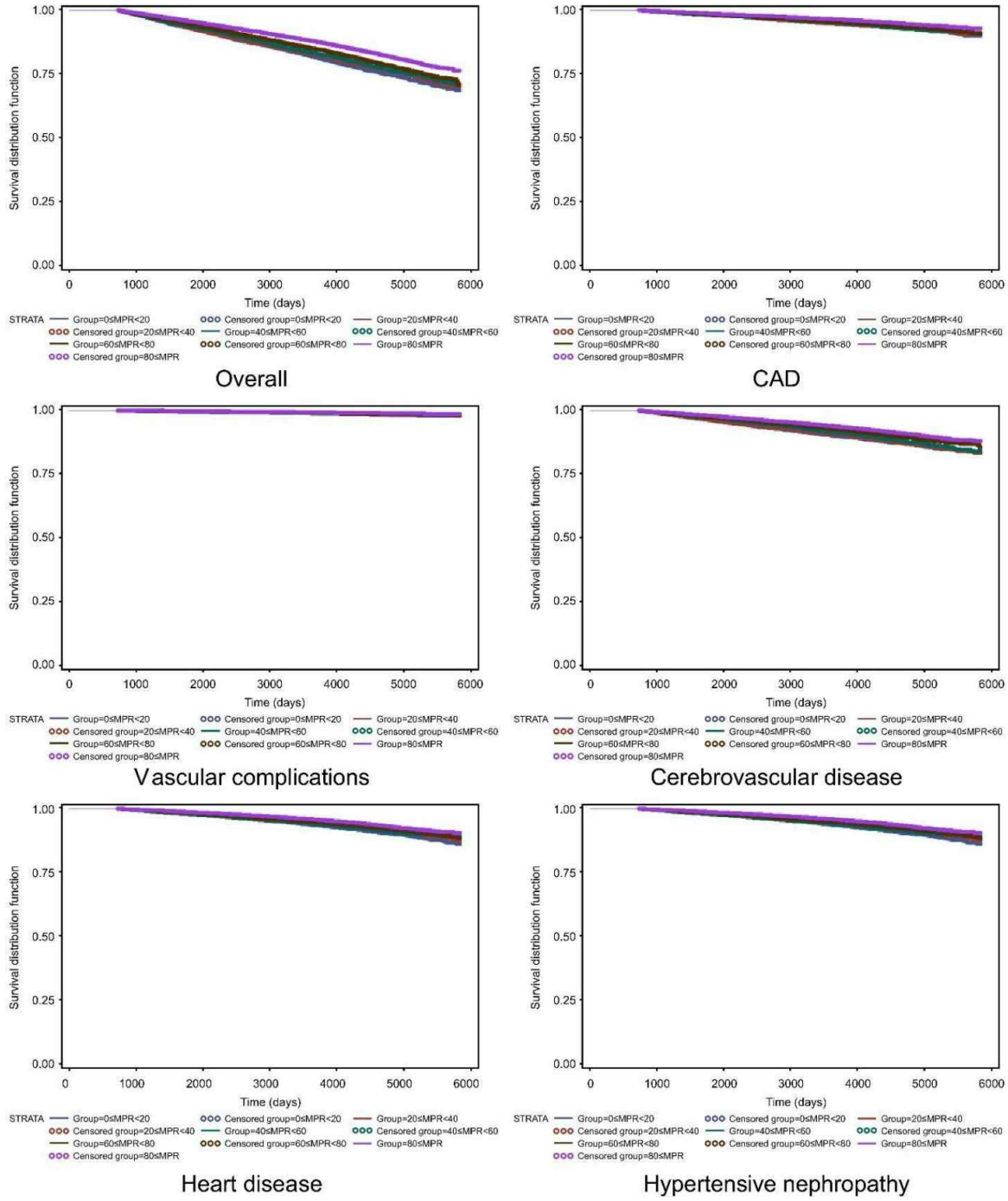
N, Number; COC, continuity of care; MPR, Medication Possession Ratio; HR, hazards ratio; CI, confidence interval; IR, Incidence rate; PYR, Person Years at Risk

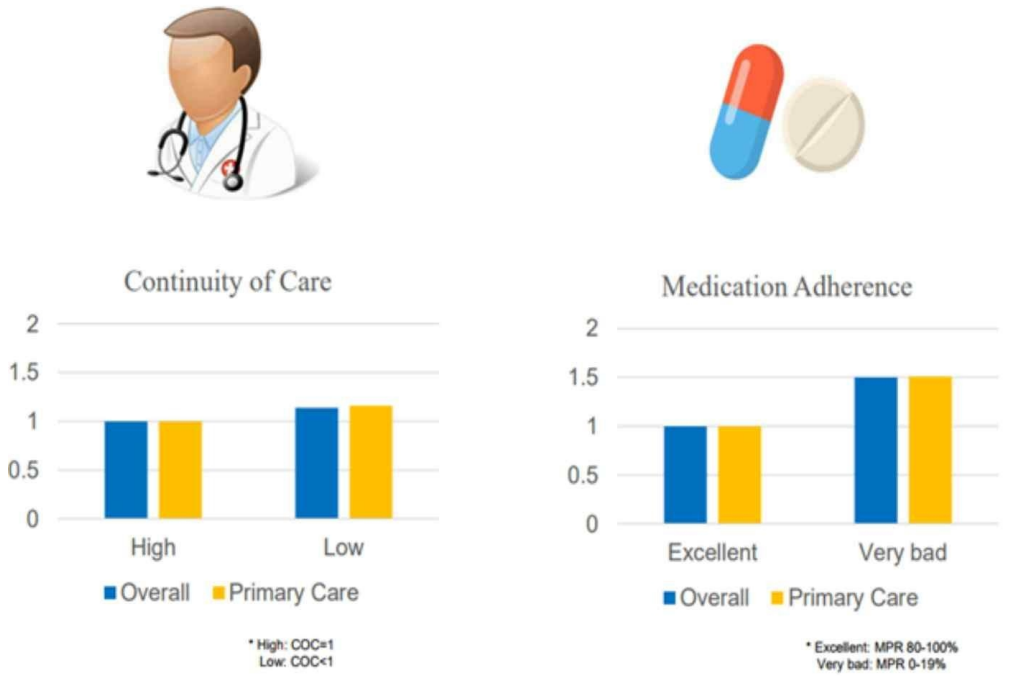
***Significance at p < .001.

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





294x227mm (120 x 120 DPI)

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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-19
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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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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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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

ABSTRACT

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

Design: A national population-based retrospective cohort study.

Setting: Secondary data analysis using National insurance claims data at all levels of hospitals in South Korea.

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

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

Results: The average level of COC in the hypertension group was 0.8112. The average proportion of the MPR in the hypertension group was 73.3%. Continuity of care in patients with hypertension showed varying results: the low COC group had a 1.14-fold increased risk of medical complications compared to the high COC group. In terms of the level of MPR in patients with hypertension, the 0–19% MPR group had a 1.5-fold risk of medical complications relative to the 80–100% MPR group.

Conclusions: In patients with hypertension, high continuity of care and medication adherence for the first 2 years of diagnosis can help prevent medical complications and promote patients' health. Therefore, effective strategies to improve continuity of care and medication adherence are required. Future research should include some factors that may affect the incidence of hypertensive complications, such as familial aggregation, and hazard stratification by the level of blood pressure, which were not considered in this study.

Therefore, there may be residual confounding and still room for improvement.

Keywords: ambulatory care-sensitive conditions, continuity of care, hypertension, medication adherence, retrospective cohort

Strengths and limitations of this study

- The study had a long follow-up period (18 years) and included over 100,000 participants, which are regarded as indicators of relatively higher reliability and validity in cohort studies according to the European Society of Cardiology.
- The utilised database contained data on health service use of over 50,000,000 Korean citizens' (99.7% of whole population), indicating that it was nationally representative.
- Hypertension (International Classification of Disease-11 code: I.10) was selected from the Ambulatory Care-Sensitive Conditions list in the Agency of Health Research and Quality standard and hypertensive complications were selected according to the definitions from World Health Organization and the advice from specialists in internal medicine.
- Owing to the retrospective nature of the study, the possibility of bias, including misclassification bias, may not be excluded.
- Some factors that may affect the incidence of hypertensive complications, such as familial aggregation, and hazard stratification by the level of blood pressure were not considered.

INTRODUCTION

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

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

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

and consultation between a patient and physician, and the MPR refers to the compliance rate of medications as prescribed by a physician. Therefore, these two measurements are broadly used for the evaluation of the ACSCs management.

Several studies have focused on hypertension, continuity of care, and medication adherence (10-12). However, the study design of previous studies was limited by the setting, and the small number of patients included (10-12). This study used the National Health Insurance Service (NHIS) database, in which over 50 million patients are registered (13). Patient data include physician visit information and the prescription data for each visit (13). As national health insurance is mandatory for every citizen in South Korea, the reliability of the data is high, and data are representative of the population on a national level (13).

The objective of this study was to analyse the effect of providing timely and effective ambulatory care to patients with early hypertension on preventing the occurrence of medical complications using COC and the MPR as indicators of effective care. The secondary objective was to assess the outcomes of hypertension according to the level of hospital at which patients were treated.

METHODS

This national, population-based, retrospective cohort study investigated the incidence of hypertension from 1 January 2002 to 31 December 2019 among the general population in South Korea. We analysed the secondary data using national insurance claims data at all levels of hospitals in South Korea. Unlike previous studies on the risk of complications according to the continuity of care and medication adherence, this study examined the time variance, including the time from the first visit to initial 2 years of the medical institution, and limited the patient's age (>30 years) (14).

Inclusion and exclusion of participants

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

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

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

guidelines on ACSCs research (n=8,907) to avoid unequal baseline characteristics; those who died within 2 years of the index date (n=1,065) for the washout period of mortality and severity; and patients who visited medical institutions less than four times after the index date (n=22,308) to enable proper measurement of COC. After these exclusions, retrospective data of 102,519 patients (out of 1.4 million members of the general population of South Korea) were included in the analysis (Figure 1).

Measurements

Continuity of care was defined as 'continuance of care by a healthcare provider to meet a patient's medical needs providing high quality and harmonised care' (17). Additionally, with a good level of continuous care provided by the physicians, the hospitalisation rate, prevalence, and the number of medical visits are reduced (18). Methods for measuring continuity of care include the COC, Usual Provider of Care index, Most Frequent Primary Care, and the Modified Continuity Index (19). We utilised COC as an indicator.

Shortell identified four core factors required for COC (20). First, the data should be of individuals. Second, analysed data should be distinguished and compared when individuals visit different medical institutions and providers. Third, COC should reflect the total number of visits for care. Finally, appropriate referral patterns should also be considered (21). South Korea has a fee-for-service system without a proper referral system (21).

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

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

N=total number of ambulatory care

n_j=number of visits to provider

M=total number of provider

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

Medication adherence refers to the degree of compliance with medications prescribed by a physician. Accurate tracking of prescription data is essential for analysing medication adherence as well as effectively predicting healthcare costs and utilisation (22). To measure medication adherence, the MPR and proportion of days covered are usually used for analysis (12). The formula for MPR is:

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

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

The major limitation of MPR estimation is that it is based on retrospective data review, and patients may have received unrecorded medication. However, owing to the Korean pharmaceutical information system, unrecorded prescriptions cannot occur in NHIS data (12). Another limitation of the MPR method is sharing medicine between family members. However, sharing of medication is likely to be minimal, because each medical appointment is scheduled according to the number of days of medication prescribed in South Korea. The major strength of the MPR method is that by researching diseases containing data on changeable parameters, such as blood pressure, HbA1c, fasting blood glucose, researchers

can closely estimate patient health status based on the drugs that they are prescribed. We received professional advice from specialists in internal medicine and cardiology for the selection of antihypertensive drugs and its list (Supplementary Table 1).

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

Statistical analysis

Explanatory variables influencing COC, MPR, and the occurrence of complications in patients with hypertension included sex, age, insurance type, income, outpatient status, COC, MPR level of the patient, number of visits, number of providers, main medical institution, and comorbidities. Patients without values for any of these variables were excluded. Subgroup analysis was performed for primary care visits to assess the efficiency of the healthcare system in South Korea. The statistical significance of differences between the groups was assessed using Student's t-test and analysis of variance. P-values <0.05 were regarded as statistically significant. The Kruskal–Wallis test and Wilcoxon rank-sum test were used to compare continuous variables that were not normally distributed, and Fisher's exact test was used to compare categorical variables between the groups.

Insurance type is divided into two categories: health insurance beneficiaries and medical aid recipients. The national health insurance system in South Korea enables medical aid recipients to obtain free health services because it is based on the lowest level of household income. Income was divided into 10 categories as described in Supplementary Table 2.

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

Most COC-related research in South Korea uses this standard because the overall levels of COC in South Korea are high compared with those in other countries. According to Organization for Economic Cooperation and Development (OECD) statistics on healthcare utilisation, South Korea has a three-fold higher outpatient and inpatient medical care use than the OECD average (23). In this study, the mean COC index was 0.8112, confirming the high level of COC in South Korea. In previous studies, the MPR has generally been divided into three categories (>80%, 50–80%, and <50% of MPR) or two categories (>60% and <60% of MPR) (24, 25). However, we decided to use five categories (excellent: 80–100%, good: 60–80%, normal: 40–60%, bad: 20–40%, and very bad: 0–20%) to enable more detailed analysis of the MPR. Outpatient status, number of visits, number of providers, and main medical institution are required factors for calculating the COC level.

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

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

Categorical variables associated with the level of COC (low vs high), were compared using the chi-square test. A comparison of complications according to the COC and MPR was performed using Kaplan–Meier survival curves and log-rank tests. The differences in medical complications according to COC and MPR were examined. The Cox proportional hazards model was used to compare the risk. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards regression.

Ethical issues

Ethics approval for the study was obtained from the Institutional Review Board at Korea University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required owing to the retrospective nature of the study. The study has been prepared in accordance with the STROBE guidelines. This study was conducted in accordance with the Declaration of Helsinki.

Patient and public involvement

We did not involve patients and public in this study because it was a retrospective study using data from the NHIS database.

RESULTS

The average COC level in the hypertension group was 0.8112. The average MPR in the hypertension group was 73.3%.

General characteristics of patients with hypertension

The patient characteristics are shown in Supplementary Table 1. Of the patients, 51,522 (50.3%) were male and 50,997 (49.7%) were female. The over 80year age group was the largest age group (27.0%), followed by the 70–-79 year (21.5%) and 60–69-year (18.1%) age groups. The vast majority of patients (94.0%) were covered by national health insurance. The largest income categories were the 9th–10th decile (27.0%), followed by the 7th–8th decile (21.5%) and the 5th–6th decile (18.1%). The most common outpatient visit categories were 7–9 visits (29.7%), followed by 10–12 visits (29.5%), and ≥13 visits (25.0%). Of the patients, 50.9% visited only one provider and 31.0% visited two providers. The majority of patients

visited clinics (70.8%). The most common comorbidities were dyslipidaemia (49.8%) and diabetes (28.7%). Approximately half the patients (50.9%) had a high level of COC. The majority of patients (55.5%) had an excellent MPR. The most frequent years of diagnosis were 2004 (10.1%), 2005 (12.1%), and 2006 (10.1%).

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

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

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)	*p*
High	52,179	7,143	15.4	Ref	
Low	50,340	8,142	17.7	**1.14 (1.10–1.17)*** **	**<0.001**

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

[a] Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and Comorbidities

***, $p<0.001$

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

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)	*p*
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**

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

[a] Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and Comorbidities

***, $p<0.001$

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

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

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)****
	p	-	**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)
	p	-	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)*****
	p	-	**<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)*****
	p	-	**<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)
	p	-	0.367

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

[a] Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and Comorbidities

**, $p<.01$ ***, $p<0.001$

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)*** **
	p	-	**<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)*** **
	p	-	**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)*** **
	p	-	**<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)*** **
	p	-	**<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)*** **
	p	-	**<0.001**	**<0.001**	**<0.001**	**<0.001**

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

[a] Adjusted for sex, age, insurance type, income, number of visits, number of providers, level of hospital, and Comorbidities

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

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

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

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

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

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

Subgroup analysis of risk of medical complications according to the COC and MPR levels in primary care clinics

A subgroup analysis of the risk of medical complications according to the COC level and MPR in patients with hypertension attending primary care clinics showed that the risk of developing complications was significantly higher in the low than in the high COC group (HR: 1.16, 95% CI: 1.12–1.21). Compared with the excellent MPR group, the risk of

developing hypertensive complications was significantly higher in the good, normal, bad, and very bad MPR groups. Compared with patients who had 4–6 visits, the risk of developing medical complications was significantly lower in patients with 7–9, 10–12, or ≥13 visits (Supplementary Table 3).

DISCUSSION

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

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

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

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

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

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

However, this study also had several limitations. First, as only the continuity of care and medication adherence in the initial 2 years were measured, follow-up after 2 years was not reflected in the effects of changes in care. Second, the risk of complications or blood pressure level was not analysed in this study. Third, whether other underlying diseases or external factors may affect the results, such as familial aggregation, the levels of blood pressure, and over-prescription of drugs, of this study could not be fully excluded. Fourth, owing to the retrospective nature of this observational study, misclassification or recall bias may impact the

validity of this study. Finally, this study can be elevated to mortality or factor study. The case–control or prospective cohort study to elucidate the association between COC, MPR levels, and the mortality of patients with hypertensive complications with its characteristics.

There are several policies for the management of ACSCs worldwide. For example, there are policies for diabetes, cervical cancer, and asthma in Australia and policies for depression, cancer, and asthma in the UK and USA; it is possible to provide primary care in a timely manner and manage chronic diseases more efficiently by including more diseases subject to chronic disease management in the ACSCs (30). Therefore, a follow-up study on the differences in the risk of complications according to changes in care should be conducted in the future.

This study sheds light on the association between continuity of care and medication adherence and the incidence of hypertensive complications, such as coronary artery disease and heart disease. The continuous management of blood pressure can be beneficial to prevent hypertensive complications among patients with hypertension. The implication should be based on subgroup analysis (Supplementary file).; visiting primary care facilities is adequately beneficial to patients with hypertension. Therefore, the Korean government should establish health policies related to chronic diseases that need management with a view to long-term care. Moreover, because of its unique structure (lack of a gatekeeper system [referral system]), the healthcare system of South Korea is facing a financial shortage. Future studies should compare the cost-effectiveness of care provided by different types of medical institutions, such as general hospitals and clinics.

Authors' contributions

Conceptualisation: Dayea Kim, Methodology: Dayea Kim, Software: Dayea Kim, Data curation: Dayea Kim, Writing – Original draft preparation: Jaewoo Cha, Visualisation: Jaewoo

Cha, Investigation: Dayea Kim, Jaewoo Cha, Supervision: Jaewoo Cha, Validation: Jaewoo Cha, Writing – Reviewing and editing: Dayea Kim, Jaewoo Cha

Competing interests

None declared.

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Data sharing statement

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

Ethics statements

Ethics approval for the study was obtained from the Institutional Review Board at Korea University (IRB document no. KUIRB-2021-0333-01). Informed consent was not required due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

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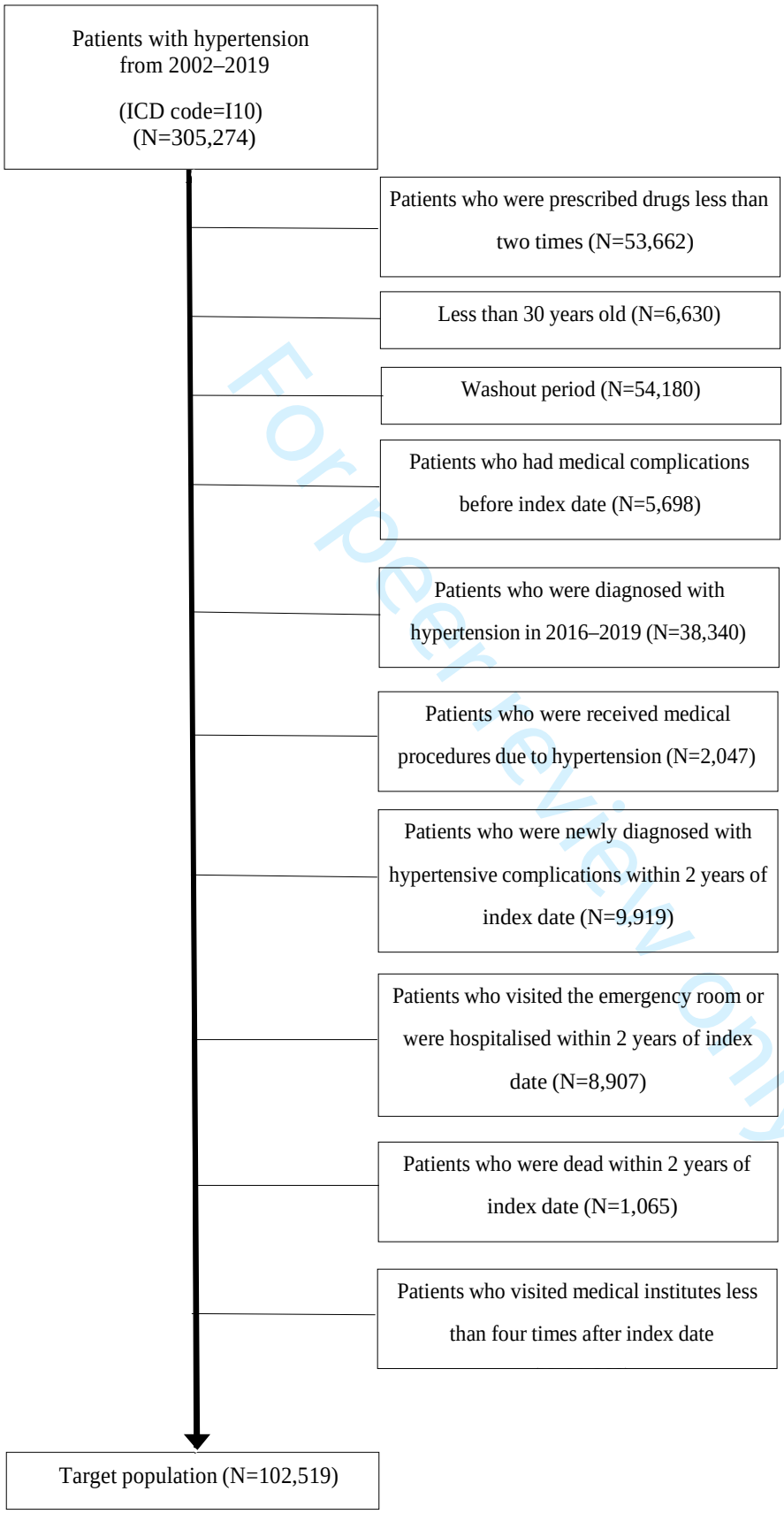
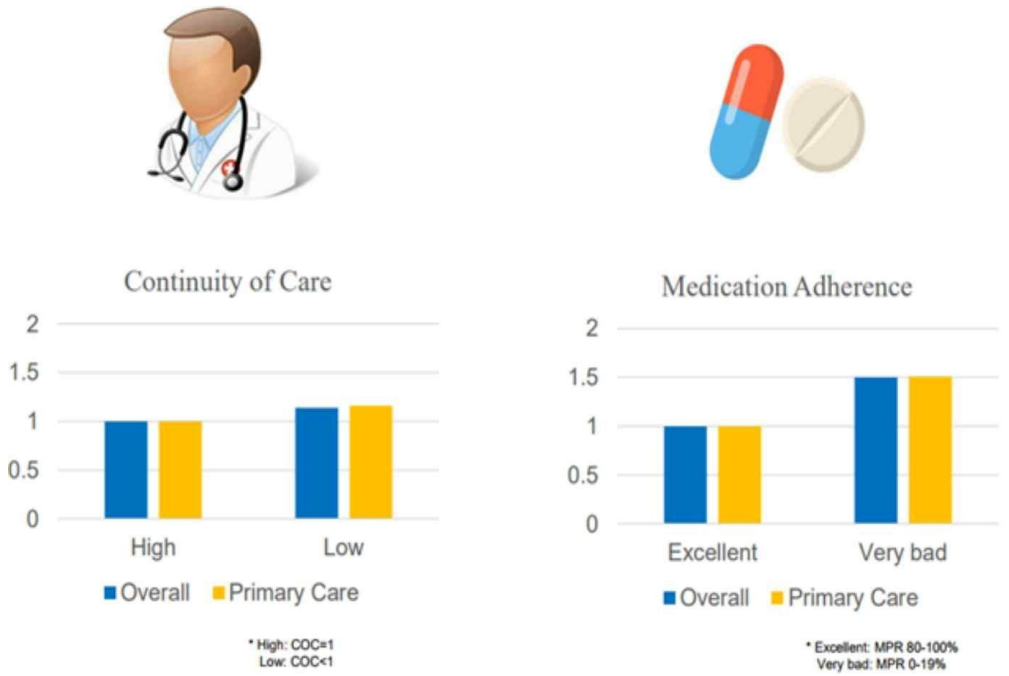
Figure legend

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.

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

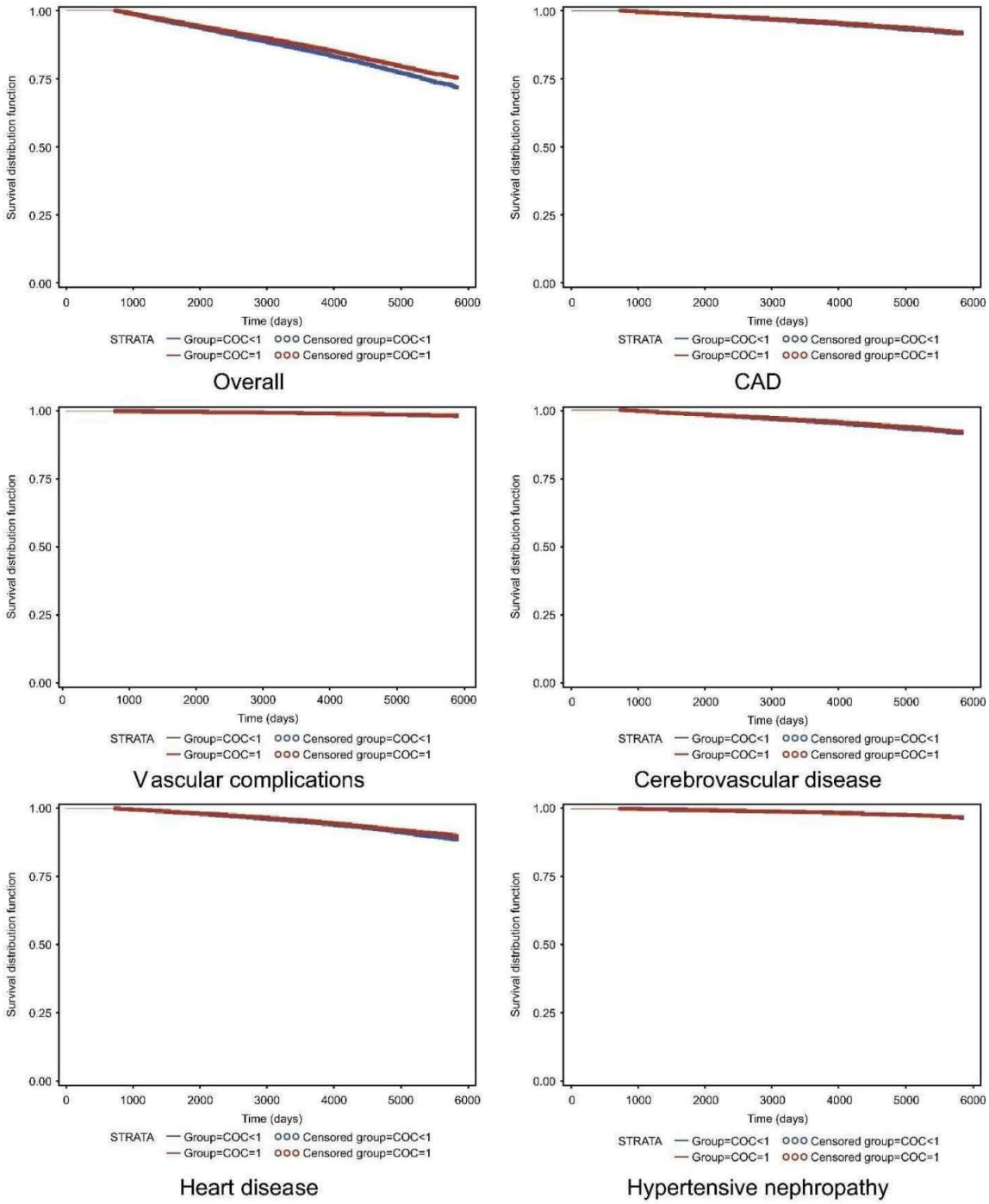
COC, continuity of care; N, number; MPR, medication possession ratio

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

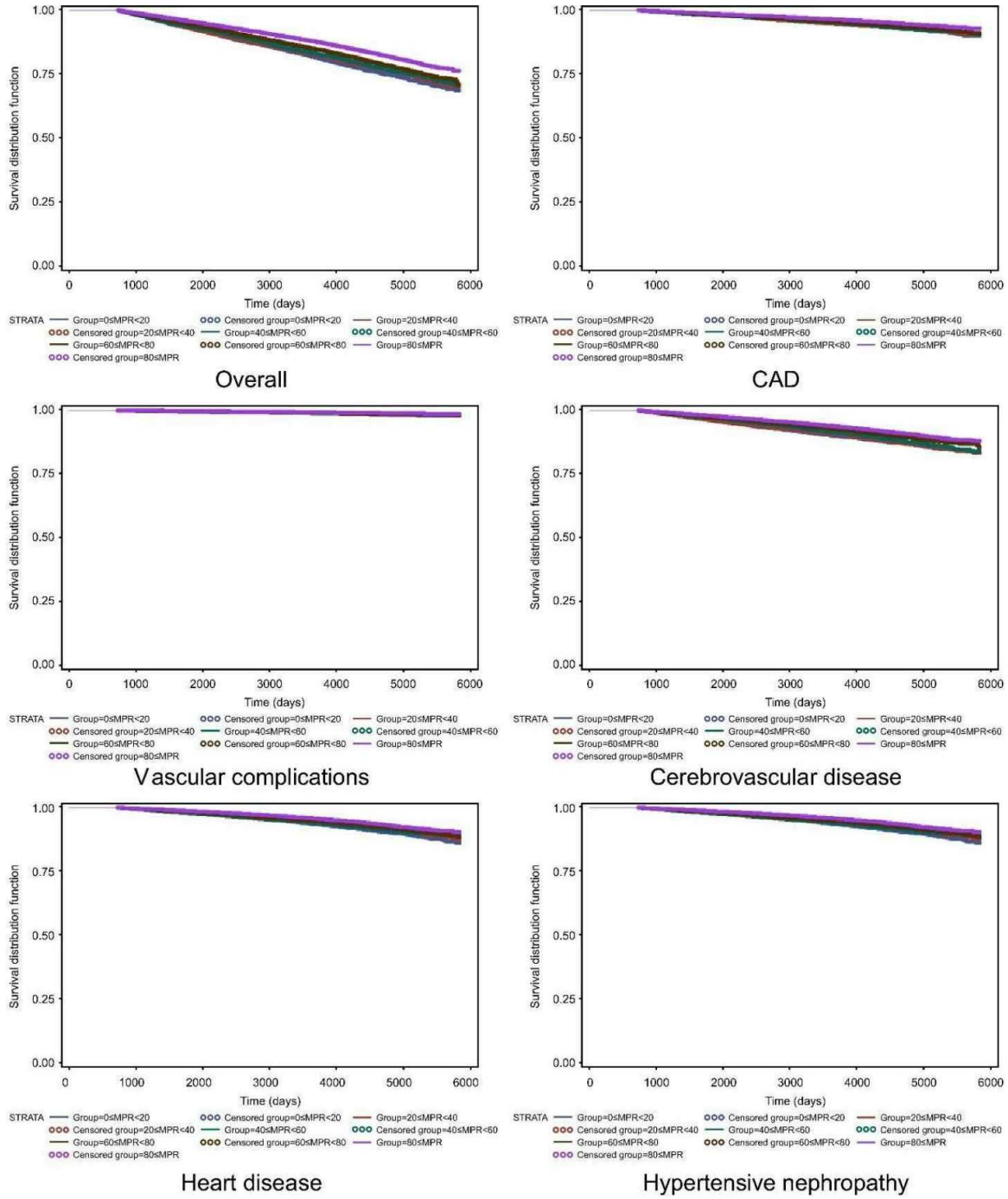
	Hazard Ratio				
	Patients	Events (N)	IR per 1000PYR	HR (95% CI)	*p-value*
COC level					
High	36,273	4,437	13.8	Ref	
Low	36,339	5,405	16.2	**1.16 (1.12–1.21)*****	**<0.001**
MPR Level					
Excellent	41,414	4,674	12.8	Ref	
Good	11,326	1,738	16.1	**1.21 (1.15–1.28)*****	**<0.001**
Normal	7,953	1,362	18.1	**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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11–18
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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.