Medication Adherence and the Risk of Cardiovascular Mortality and Hospitalization Among Patients With Newly Prescribed Antihypertensive Medications

Soyeun Kim, Dong Wook Shin, Jae Moon Yun, Yunji Hwang, Sue K. Park, Young-Jin Ko, BeLong Cho

Abstract—The importance of adherence to antihypertensive treatments for the prevention of cardiovascular disease has not been well elucidated. This study evaluated the effect of antihypertensive medication adherence on specific cardiovascular disease mortality (ischemic heart disease [IHD], cerebral hemorrhage, and cerebral infarction). Our study used data from a 3% sample cohort that was randomly extracted from enrollees of Korean National Health Insurance. Study subjects were aged ≥20 years, were diagnosed with hypertension, and started newly prescribed antihypertensive medication in 2003 to 2004. Adherence to antihypertensive medication was estimated as the cumulative medication adherence. Subjects were divided into good (cumulative medication adherence, ≥80%), intermediate (cumulative medication adherence, 50%–80%), and poor (cumulative medication adherence, <50%) adherence groups. We used time-dependent Cox proportional hazards models to evaluate the association between medication adherence and health outcomes. Among 33 728 eligible subjects, 670 (1.99%) died of coronary heart disease or stroke during follow-up. Patients with poor medication adherence had worse mortality from IHD (hazard ratio, 1.64; 95% confidence interval, 1.16–2.31; *P* for trend=0.005), cerebral hemorrhage (hazard ratio, 2.19; 95% confidence interval, 1.28–3.77; *P* for trend=0.004), and cerebral infarction (hazard ratio, 1.92; 95% confidence interval, 1.25–2.96; *P* for trend=0.003) than those with good adherence. The estimated hazard ratios of hospitalization for cardiovascular disease were consistent with the mortality end point. Poor medication adherence was associated with higher mortality and a greater risk of hospitalization for specific cardiovascular diseases, emphasizing the importance of a monitoring system and strategies to improve medication adherence in clinical practice. (***Hypertension***. **2016;67:506-512. DOI: 10.1161/HYPERTENSIONAHA.115.06731.)** ● **Online Data Supplement**

Key Words: antihypertensive agents ■ cerebral hemorrhage ■ hospitalization ■ medication adherence ■ stroke

Cardiovascular diseases (CVDs) are a leading cause of death in the world. High blood pressure contributes to ≈54% of stroke and 47% of IHD worldwide.[1] Managing blood pressure in hypertensive patients is important for the prevention of CVD and the reduction of mortality.[2,3] The use of antihypertensive drug therapy reduces the risk of stroke by an estimated 34% and the risk of IHD by 21%.[4]

The definition of medication adherence is that patients take their medications as prescribed, as well as continuing to take a prescribed medication based on the treatment alliance established between the patient and the physician.[5] Adherence to medication among patients with chronic diseases is suboptimal, dropping most dramatically during the first year after the start of therapy.[6,7] For example, half of the patients who are prescribed an antihypertensive drug will discontinue their medication within 1 year of starting the therapy.[8–10] Patients with chronic diseases require a good partnership with their physician in order to achieve the long-term outcome goal.

Patients who are adherent to antihypertensive drugs are more likely to achieve blood pressure control. A meta-analysis reported that patients adherent to antihypertensive medications showed better blood pressure control, compared with those who were nonadherent (odds ratio, 3.44; 95% confidence interval [CI], 1.60–7.37).[11] Evidence is mounting that patients who show poor adherence to antihypertensive medication have a higher risk of adverse outcomes, including all-cause hospitalization and CVD hospitalization,[12,13] and they have higher healthcare costs[14] compared with patients with good adherence.[12,13,15] A recent cohort study[15] reported that a good-adherence group had a significantly lower incidence of acute cardiovascular events, compared with a group with poor adherence to antihypertension medication (hazard ratio [HR],

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0.62; 95% CI, 0.40–0.96). Pittman et al[16] also reported that patients with a medication adherence of ≥80% decreased their risk of CVD-related hospitalization by 33% (odds ratio, 1.33; 95% CI, 1.25–1.41) and emergency department visits by 45% (odds ratio, 1.45; 95% CI, 1.33–1.58). However, few investigations have been conducted into the effect of adherence on all-cause mortality or all-CVD mortality,[17] while there has been no study of the association between medication adherence and specific CVD mortality. Furthermore, only a few studies of antihypertensive medication adherence have been carried out in Korea. The good-adherence rate (cumulative medication adherence [CMA], ≥80%) among hypertensive Korean patients was <40% during the first year after starting the antihypertensive therapy.[10] Medication adherence seemed to be related to sex, disability, residential area, the medical provider who prescribed the medication, the type of antihypertensive agent prescribed, the number of agents used, and the number of comorbidities that a patient had.[10,18,19] In a cohort study using the Korean National Health Insurance Claims Database (KNHICD), nonadherence to antihypertensive therapy increased all-cause mortality and the risk of hospitalization for CVD (HR, 1.57; 95% CI, 1.40–1.76).[12] However, this study did not include the patients' cause of death and hence was not able to evaluate specific CVD mortality among the Korean population.

The objectives of this study were to evaluate the effect of adherence to antihypertensive medication on specific CVD mortality, as well as all-cause mortality and hospitalization for CVD, among patients with newly diagnosed hypertension.

Methods

Data Source

We used a cohort that was randomly selected as 3% of the total KNHICD (n=1 025 340), starting on December 31, 2002 and maintained until December 31, 2010.The Korea National Health Insurance (KNHI) program provides mandatory health insurance, offering coverage of medical care services to ≈100% of Koreans; 97% of Koreans are covered by Medicare and 3% are covered by Medicaid. Medical services on fee-for-service basis are provided by private providers and which is then reimbursed by the KNHI. A 30% of copayment is applied for most nonsevere diseases of Medicare subscribers. Medicaid beneficiaries in the lowest income bracket were provided medical services for mostly free. The records of medical services and prescribed medication covered by KNHI are collected in the KNHICD.

The cohort data include qualification data, medical services claim data, and pharmacy claim data. Qualification data include patients' KNHI identification number, sex, age, disability, household income, residential regions, type of insurance, and mortality information (patients' cause of death, and year and month of death: this database does not contain date of death). Medical services claim data contain information about the inpatient or outpatient services an individual receives, such as diagnosis information classified by the *International Classification of Diseases*, Tenth Revision (ICD-10), recoded by physicians, or the codes of treatment provided to patients, dates of hospital visits, length of stay in hospital, and healthcare costs. Pharmacy claims data consist of patients' disease codes, name of medication, the date that each prescription was generated and filled, the number of total days' pills supplied per visit, the dosage, and the cost of medication. Qualification data were linked to medical service data and pharmacy claims data by the identification code.

Study Subjects

We defined the study population as subjects who were aged ≥20 years, were newly diagnosed with hypertension (ICD-10: I10, I11, I12, I13, or I15), and were newly treated with at least one of the possible medications, including calcium channel blockers (Anatomic Therapeutic Chemical [ATC] classification code C08, diuretics [ATC code C03], angiotensin-converting enzyme inhibitors [ATC code C09], angiotensin receptor blockers [ATC code C09], β-blockers [ATC code C07], or other antihypertensive drugs [ATC code C02] in 2003 to 2004. We confirmed that the study subjects did not have any previous record of antihypertensive medication during the previous 12 months. We excluded any patient who had been diagnosed with IHDs (ICD-10: I20–I25), cerebrovascular diseases (ICD-10: I60–I64), or heart failure (ICD-10: I50) before 2003.

On the basis of the above criteria, out of the total cohort (n=1 025 340), 38 170 subjects were eligible for the study. Among these, only patients who had their prescriptions filled more than twice during 2 years were included, because CMA can only be calculated when patients have multiple prescriptions filled. Patients who died within 2 years after the first visit were also excluded from the study population in order to ensure a sufficient observation time interval for adherence assessment. On the basis of these criteria, 33 728 patients were finally selected for the analyses (Figure). Subjects were followed up from the date of first diagnosis until death, hospitalization for CVD, or the end of the study period (December 31, 2010).

Assessment of Adherence

Adherence to a medication was assessed using the CMA scale, based on pharmacy claims data.[20–22] This proportion was calculated as the sum of the days of medication supplied (obtained over a series of intervals) divided by the total treatment duration (days), as derived from the dates of the first and last prescriptions dispensed.[18,20,21] Pills from the last prescriptions were not included because their consumption was unknown.[23] The 80% cutoff was previously used in related studies.[10,18,24] For analytic purposes, we classified drug adherence into 3 groups according to CMA level: good (CMA≥80%), intermediate (50% ≤ CMA < 80%), and poor (CMA<50%).

Outcomes

CVD was defined as a composite end point of acute myocardial infarction (AMI, ICD-10: I21–I23) and other IHD, including angina pectoris (ICD-10: I20, I24, and I25) or cerebrovascular events, such as cerebral hemorrhage (ICD-10: I60–I62), cerebral infarction (ICD-10: I63), and other stroke (ICD-10: I64, I67, and I69). IHD was defined as a composite end point of AMI and other IHD (ICD-10: I20-25). Stroke was defined as all cerebrovascular events (ICD-0: I60–I64, I67, and I69).

The primary outcome of the study was specific CVD mortality and all-cause mortality during follow-up. Vital status, cause of death, and date of death were identified by matching the qualification data of the KNHICD with the National Statistical Office death registry and including the cause of death from death certificates. Secondary outcomes were the incidences of first-ever CVD events during follow-up. The onset of any CVD was identified only from inpatient hospital claim records to minimize bias from overcoding.

Statistical Analysis

The baseline characteristics of hypertensive patients according to their first 2 years adherence to antihypertensive medication were described using frequencies and percentages, or median with interquartile range.

The follow-up time was the period between the date of diagnosis for hypertension and the date of death, or date of first hospitalization for CVD outcomes, or December 31, 2010. The index date was defined as the date of the initial diagnosis of hypertension and the first prescription date of antihypertensive medication. We calculated CMA across the entire observation period. To consider the changes of medication adherence over time, CMA was calculated for a 2-year interval from the index date to end date of follow-up. To evaluate the

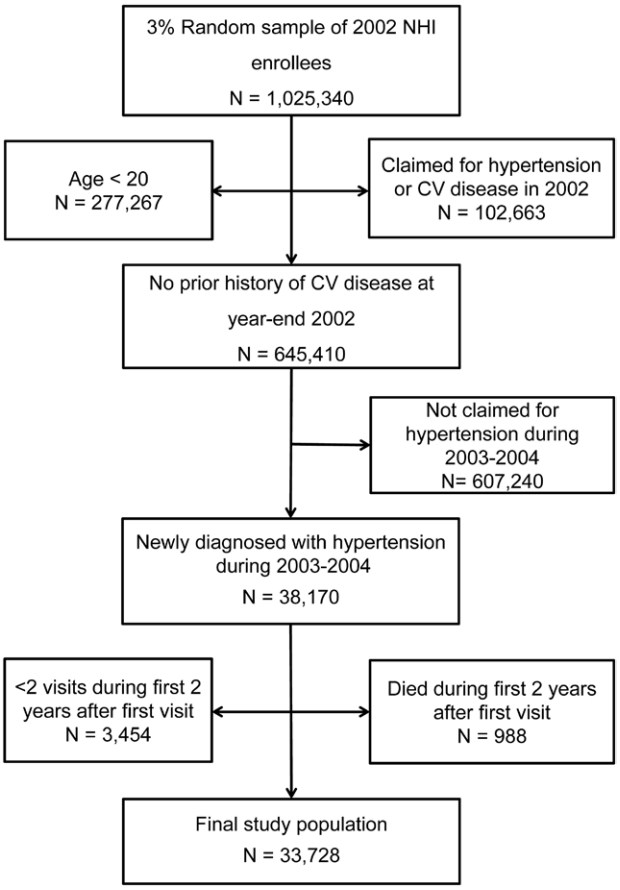

Figure. Flow chart showing inclusion and exclusion criteria for the selected study population. CV indicates cardiovascular; and NHI, National Health Insurance.

long-term cumulative effect of blood pressure control,[25] we defined the CMA of the second 2-year interval as the mean of the first and second interval CMA values. Similarly, the CMA of the third 2-year interval was calculated as the mean of the first, second, and third interval CMA values.

We used time-dependent Cox proportional hazards models to calculate HRs between the level of adherence to antihypertensive medication and the adverse health outcomes. The HRs represented the risk of CVD mortality, all-cause mortality, or hospitalization for CVD, in relation to CMA (good adherence was regarded as the reference value). All multivariate models were adjusted for age, sex, income level, residential regions, diabetes mellitus, dyslipidemia, Charlson comorbidity score,[26] and the number of antihypertensive medications included in the first prescription at the index date. Patients who were diagnosed with diabetes mellitus or dyslipidemia and were prescribed antihyperglycemic or antihyperlipidemic medication within the past year from the index date were defined as having diabetes mellitus or dyslipidemia. The information about diabetes mellitus, dyslipidemia, and Charlson comorbidity score were assessed for the period between the dates 1 year before the index date and the end of the study period.

We performed additional analysis with the subset which never been hospitalized for non-CVD during the study period (n=12 991, 38.5%) to consider the effects of changes in medication adherence for non-CVD hospitalization.

Analyses were performed using the statistical software package STATA version 13 (Stata Corp, College Station, TX). All tests were 2-sided, and statistical significance was defined as a P value <0.05.

Ethics Statement

This study was approved by the Institutional Review Board of Seoul National University. The requirement for informed consent was waived because the study was based on routinely collected administrative or claims data.

Results

Subject Characteristics

Of the 33 728 subjects included in the study, 15 709 were men and 18 019 were women. Among these, 2519 (7.5%) died during follow-up including 581 (1.72%) deaths from IHD or stroke after the date when they received their first prescription for antihypertensive agents. Subjects were classified according to their CMA level as 12 316 (31.3%) good, 10 568 (32.2%) intermediate, and 10 844 (32.2%) poor adherence.

Table 1 shows the baseline characteristics of the hypertensive patients according to medication adherence in the first 2 years. At baseline, the median CMAs were 91% in good, 69% in intermediate, and 33% in poor adherence group, respectively. More than 70% of patients were aged ≥50 years and 53% were women. The majority of patients lived in a metropolitan or city area. Calcium channel blockers (38.5%) were the most commonly prescribed first antihypertensive medications, followed by β-blockers (15.6%), diuretics (14.7%), angiotensin-converting enzyme inhibitors (9.8%), and angiotensin receptor blockers (9.3%). More than 60% of the study subjects did not have any disease comorbidities (63.2%), whereas 33% of the study subjects had diabetes mellitus.

Adherence to Antihypertensive Medications and CVD Mortality

Of the 33 728 patients with newly prescribed antihypertensive medication, 379 patients died from stroke, and 202 died from IHD. CVD and all-cause mortality were inversely associated with antihypertensive medication adherence, as shown by the P for trend values (Table 2). The risk of stroke mortality increased with decreasing medication adherence (intermediate: HR, 1.68; 95% CI, 1.30–2.18 and poor: HR, 1.92; 95% CI, 1.47–2.50; P for trend<0.001). The mortality risks of the individual end points, including IHD, cerebral hemorrhage, and cerebral infarction, were also increased, similarly to the outcome of all-cause mortality. This correlation remained robust even after adjustment for covariates, taking into account the potential confounders in the multivariate model (Table 2).

Among nonhospitalization subset (n=12 991, 38.5%), poor medication adherence was associated with higher all-cause mortality (intermediate: HR, 1.47; 95% CI, 1.16–2.86 and poor: HR, 1.71; 95% CI, 1.33–2.18; P for trend<0.001). The results for all-CVD mortality were also consistent (intermediate: HR, 1.28; 95% CI, 0.87–1.87 and poor: HR, 1.65; 95% CI, 1.11–2.46; P for trend=0.013; Table S1 in the online-only Data Supplement).

Adherence to Antihypertensive Medications and Hospitalization for CVD

The risk of hospitalization for CVD (AMI, IHD, cerebral hemorrhage, and cerebral infarction) increased stepwise with decreasing adherence, as shown by the P for trend values (Table 3). The HRs for the risk of hospitalization for cerebral hemorrhage were estimated as 1.25 (95% CI, 0.94–1.67) for

Table 1. Characteristics of the Study Population (n=33 728)

Characteristics	n (%)
Sex	
Men	15 709 (46.6)
Women	18 019 (53.4)
Age, y	
<50	9493 (28.1)
50–59	8722 (25.9)
60–69	9772 (29.0)
≥70	5741 (17.0)
Income level	
Low	12 918 (38.3)
Middle	10 544 (31.3)
High	10 266 (30.4)
Residence	
Metropolitan	14 973 (44.4)
City	13 554 (40.2)
Rural	5201 (15.4)
Type of insurance	
Medicare	33 399 (99.0)
Medicaid	329 (1.0)
Charlson comorbidity score	
0	21 324 (63.2)
1	7613 (22.6)
2	3167 (9.4)
≥3	1624 (4.8)
Diabetes mellitus	
No	22 611 (67.0)
Yes	11 117 (33.0)
Dyslipidemia	
No	29 994 (88.9)
Yes	3734 (11.1)
No. of antihypertensive medications taken	
1	13 243 (39.3)
2	12 414 (36.8)
≥3	8071 (23.9)
Prescribed antihypertensive medication	
CCB	12 983 (38.5)
β-Blocker	5248 (15.6)
Diuretics	4947 (14.7)
ACEI	3312 (9.8)
ARB	3123 (9.3)
Cumulative medication adherence	
Good	12 316 (36.5)
Median, IQR	0.91 (0.86–0.96)
Intermediate	10 568 (31.3)
Median, IQR	0.67 (0.59–0.74)
Poor	10 844 (32.2)
Median, IQR	0.33 (0.19–0.43)

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; and IQR, interquartile range.

the intermediate adherence group, and 1.90 (95% CI, 1.42–2.53) for the poor adherence group (*P* for trend<0.001).

Among nonhospitalization subset (n=12 991, 38.5%), although the trend was not statistically significant, the risk of hospitalization for CVD increased with decreasing adherence (Table S2).

Discussion

This study found an association between medication adherence and disease-specific mortality (IHD, cerebral hemorrhage, and cerebral infarction), all-cause mortality, and the first hospitalization for CVD among patients newly treated with antihypertensive medication. The risk of disease-specific mortality increased progressively as adherence to medication declined. Compared with good adherence, the risk of all-CVD mortality increased stepwise from intermediate adherence (46% higher risk) to poor adherence (81% higher risk). The trend of increasing risk across the adherence groups was statistically significant (all *P* for trend values of the HRs for disease-specific mortality were <0.05). The trend in reducing the risk of mortality was more evident for stroke than for AMI or IHD. The risk of first hospitalization for CVD also increased with decreased medication adherence. The risk of hospitalization for cerebral hemorrhage was most significantly increased as adherence to antihypertensive medication decreased (poor adherence group 90% higher risk, *P* for trend<0.001). Among nonhospitalization subset, poor medication adherence was associated with higher all-cause mortality and all-CVD mortality. Although this trend was not statistically significant, the risk of hospitalization for CVD increased with decreasing adherence. Subset analysis provides further support for our finding about the association of adherence to CVD mortality.

Despite the remarkable significance of blood pressure control for the prevention of CVD and mortality demonstrated in previous studies,[3,4,27,28] at the clinical level there is still only limited evidence for an association between adherence to antihypertensive medication and clinical outcomes. Other studies found a positive relationship between medication compliance and clinical outcomes, such as the risk of all-cause mortality or CVD events,[15,29,30] reflecting the importance of maintaining optimal medication adherence. Our study demonstrated an association between adherence to antihypertensive medication and disease-specific mortality (IHD, cerebral hemorrhage, and cerebral infarction) as well as all-cause mortality. The correlation of low adherence to antihypertensive medication on cerebral hemorrhage mortality (poor adherence HR, 2.19; 95% CI, 1.28–3.77; *P* for trend=0.004) was greater than that on IHD mortality (poor adherence HR, 1.64; 95% CI, 1.16–2.31; *P* for trend=0.005). This is an original finding of this study, in that it distinguishes the association of adherence to antihypertensive medication on mortality from specific kinds of CVD.

Our study provides further support for previous findings[12,13,31] about the association of adherence to antihypertensive medication on hospitalization for CVD. Compared with those patients with good medication adherence, patients with poor adherence were 1.42× more likely to require hospitalization for AMI. The risk of hospitalization for cerebral hemorrhage increased more prominently than that for AMI

Table 2. Association Between Antihypertensive Medication Adherence and Mortality of Cardiovascular Disease, or All-Cause Death

	Good Adherence			Intermediate Adherence			Poor Adherence			
Outcome	Cohort, n	Cases, n	HR (95% CI)	Cohort, n	Cases, n	HR (95% CI)	Cohort, n	Cases, n	HR (95% CI)	*P* Trend
All-cause mortality	12316	742	1.00	10568	897	1.39 (1.26–1.53)	10844	880	1.75 (1.58–1.93)	<0.001
Acute myocardial infarction	12316	50	1.00	10568	45	1.02 (0.68–1.53)	10844	45	1.32 (0.87–1.99)	0.210
Ischemic heart disease	12316	65	1.00	10568	64	1.11 (0.78–1.57)	10844	73	1.64 (1.16–2.31)	0.005
Cerebral hemorrhage	12316	23	1.00	10568	27	1.35 (0.77–2.35)	10844	34	2.19 (1.28–3.77)	0.004
Cerebral infarction	12316	34	1.00	10568	42	1.49 (0.95–2.35)	10844	57	1.92 (1.25–2.96)	0.003
Stroke	12316	99	1.00	10568	145	1.68 (1.30–2.18)	10844	135	1.92 (1.47–2.50)	<0.001

Adjusted for age group, sex, income, Charlson comorbidity score, area of residence, no. of drugs taken, diabetes mellitus, and dyslipidemia. CI indicates confidence interval; and HR, hazard ratio.

or cerebral infarction. The results of this study are consistent with those of previous studies.[32,33]

Whereas many previous findings were restricted to patients with diabetes mellitus or with previous CVD,[34–36] few studies have reported the importance of hypertensive medication adherence in primary prevention. Most research into primary prevention found a relationship between adherence to antihypertensive medication and CVD events[12,31,32] or all-cause mortality.[17,29] Degli Esposti et al[29] showed that the risk of the combined outcome of all-cause death, stroke, or AMI decreased with an increase in medication adherence (good adherence: HR, 0.69; 95% CI, 0.58–0.81 and excellent adherence: HR, 0.53; 95% CI, 0.46–0.61). Another study reported that, compared with their low-adherence counterparts, high adherers showed a great risk reduction for CVD events among newly diagnosed hypertensive patients (HR, 0.62; 95% CI, 0.40–0.96).[15] Compared with previous studies in primary prevention, our study separately estimated the risk of CVD mortality and first hospitalization, and the duration of follow-up was longer (mean 5 years, extended ≤7 years); in addition, the study population was large and accurately represented South Korean hypertensive patients by drawing on the claim data of the KNHI.

Our study used 3 levels of adherence, whereas previous studies referred to 2 levels using a cut-off value of 0.8.[12,13,16,32,33] The division into 3 levels of medication adherence is useful for analyzing the trend of CVD risk. We used a time-dependent Cox proportional regression model in order to take into account the fact that medication adherence might change overtime during the follow-up period.[37]

Limitations

Our study has several potential limitations. First, we measured medication adherence indirectly from administrative claims data. Direct methods include directly observed therapy, measurement of the concentration of the medication or its metabolites in blood or urine, and measurement of biological markers in blood.[5] Direct approaches are more robust and accurate than indirect methods. However, it is difficult to apply direct methods to a large population. Electronic pharmacy data are more frequently used, and it is an efficient indirect method for assessing medication adherence in a large population. CMA is a well-validated measurement tool, and it is useful for measuring adherence over a long period.[20] The measurement of drug use was based on dispensed medications and actual drug-taking behaviors remain unknown. However, there is evidence to suggest a strong correlation between pharmacy claims and health outcomes.[11,38]

Second, a formal diagnosis of hypertension was not available. In this study, the prescription of a antihypertensive drug was regarded as equivalent to a diagnosis of hypertension. Thus, there was potential for misclassification. Some of the subjects treated with antihypertensive drugs may not have been truly hypertensive. Studies on the validity of hypertension diagnosis using the KNHICD have not been conducted in South Korea. However, Bullano et al[39] suggested that the agreement between prescription claim data and medical record data for identifying patients with hypertension is relatively high. The sensitivity and specificity of hypertension definition using both diagnosis and prescription information from claim data were 76.2% and 93.3%, respectively, and the κ score was 0.65.[39] Other studies identified hypertensive patients as those who had at least 2 claims for outpatient services or 1 claim for hospitalization and had at least 1 prescription,[14,18] which was similar as our definition of hypertensive patients. The condition of at least 2 claims for outpatient services was included to reduce the incidence of false-positive diagnoses or misclassification.

Table 3. Association Between Antihypertensive Medication Adherence and Hospitalization for Cardiovascular Disease

	Good Adherence			Intermediate Adherence			Poor Adherence			
Outcome	Cohort, n	Cases, n	HR (95% CI)	Cohort, n	Cases, n	HR (95% CI)	Cohort, n	Cases, n	HR (95% CI)	*P* Trend
Acute myocardial infarction	12316	111	1.00	10568	108	1.12 (0.85–1.46)	10844	107	1.42 (1.08–1.87)	0.013
Ischemic heart disease	12316	393	1.00	10568	341	1.04 (0.90–1.21)	10844	301	1.37 (1.17–1.60)	<0.001
Cerebral hemorrhage	12316	90	1.00	10568	99	1.25 (0.94–1.67)	10844	106	1.90 (1.42–2.53)	<0.001
Cerebral infarction	12316	390	1.00	10568	385	1.14 (0.99–1.31)	10844	355	1.39 (1.20–1.61)	<0.001
Stroke	12316	467	1.00	10568	454	1.12 (0.98–1.28)	10844	424	1.40 (1.22–1.61)	<0.001

Adjusted for age group, sex, income, Charlson comorbidity score, area of residence, no. of drugs taken, diabetes mellitus, and dyslipidemia. CI indicates confidence interval; and HR, hazard ratio.

Third, there was a lack of clinical information on the severity of hypertension. The confounding effect of baseline blood pressure on the association between adherence and health outcome is limited. However, a meta-analysis of 147 trials showed that the magnitude of the CVD risk reduction using antihypertensive drugs was similar, regardless of pretreatment blood pressure.[3] Another randomized controlled trial suggested substantial benefit of various antihypertensive drugs even when reductions of blood pressure are small.[40] A study indicated that high adherers showed a significantly decreased risk of acute cardiovascular events, in spite of similar reductions of blood pressure levels across the adherence groups.[15] Among patients with history of CVD but without clinical defined hypertension, treatment of antihypertensive medications was associated with decreased risk of stroke, secondary CVD events, and all-cause mortality.[41] Thus, lack of blood pressure data are unlikely to have affected our analysis results.

Fourth, the KNHICD was originally constructed to facilitate reimbursement for services provided. Thus, the claims data we used did not include lifestyle adjustments among the risk factors affecting CVD morbidity and mortality, such as smoking, family history of CVD, and physical activity.

Finally, we did not consider to adjust days of non-CVD hospitalization. However, ≈85% of length of stay in hospital of our data was ≤15 days and 10% of length of that was from 15 to 30 days. Because duration of hospitalization was mostly short, medication adherence of non-CVD hospitalization is unlikely to have significantly affected our analysis. Additional analysis with subset who were never hospitalized also showed consistent our results.

Perspectives

This study is the first to assess the association of adherence to antihypertensive medication on CVD-specific mortality in South Korea. The large sample was followed up for 7 years, and this study extends the understanding of the positive impact of antihypertensive medication adherence on cardiovascular mortality, in addition to cardiovascular events. The consequences of poor adherence to antihypertensive medication extend beyond health prevention and involve the cost of CVD prevention and the economic sustainability of national health services. It is thus important to increase the awareness of health professionals about the need to improve compliance with therapy.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study is the first to assess the effect of adherence to antihypertensive medication on cardiovascular disease–specific mortality in South Korea.
- Our study separately estimated the risk of cardiovascular disease mortality and first hospitalization, and the duration of follow-up was longer (≤7 years), the study population was accurately represented South Korean hypertensive patients by drawing on the claim data of the Korea National Health Insurance.

What Is Relevant?

- This study found an association between medication adherence and disease-specific mortality (ischemic heart disease, cerebral hemorrhage, and cerebral infarction) as well as all-cause mortality among patients newly treated with antihypertensive medication.
- The mortality risks of the individual end points, including ischemic heart disease, cerebral hemorrhage, and cerebral infarction increased with decreasing antihypertensive medication adherence.
- The risk of hospitalization for specific cardiovascular disease (acute myocardial infarction, ischemic heart disease, cerebral hemorrhage, and cerebral infarction) increased with decreasing medication adherence.

Summary

The improvement of antihypertensive medication adherence extends beyond the health prevention and involves the economic sustainability of national health services. Thus, it is important to increase the awareness of health professionals about the need to improve medication adherence.

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ONLINE SUPPLEMENT

Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications

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Table S1. Association between antihypertensive medication adherence and mortality of cardiovascular disease, or all-cause death with the subset which never been hospitalized for non-cardiovascular disease during study period (N=12991)

Outcome	Good adherence			Intermediate adherence			Poor adherence			P-trend
	Cohort N	Cases N	HR (95% CI)	Cohort N	Cases N	HR (95% CI)	Cohort N	Cases N	HR (95% CI)	
All-cause mortality	5254	134	1.00	4015	139	1.47 (1.16–1.86)	3722	132	1.71 (1.33–2.18)	<0.001
All-CVD mortality	5254	53	1.00	4015	48	1.28 (0.87-1.87)	3722	50	1.65 (1.11-2.46)	0.013
Acute myocardial infarction	5254	14	1.00	4015	16	1.59 (0.77–3.27)	3722	13	1.7 (0.80–3.77)	0.144
Ischemic heart disease	5254	18	1.00	4015	17	1.30 (0.67–2.53)	3722	19	1.97 (1.02–3.82)	0.047
Cerebral hemorrhage	5254	10	1.00	4015	4	0.54 (0.17–1.72)	3722	12	2.18 (0.92–5.17)	0.110
Cerebral infarction	5254	11	1.00	4015	12	1.64 (0.72–3.75)	3722	9	1.26 (0.51–3.10)	0.544
Stroke	5254	35	1.00	4015	31	1.29 (0.79–2.09)	3722	31	1.51 (0.92–2.48)	0.097

*Adjusted for age group, sex, income, Charlson’s comorbidity score, area of residence, number of drugs taken, diabetes mellitus, dyslipidemia.

Table S2. Association between antihypertensive medication adherence and hospitalization for cardiovascular disease in the subset which never been hospitalized for non-cardiovascular disease during study period (N=12991)

Outcome	Good adherence			Intermediate adherence			Poor adherence			P-trend
	Cohort N	Cases N	HR (95% CI)	Cohort N	Cases N	HR (95% CI)	Cohort N	Cases N	HR (95% CI)	
Acute myocardial infarction	5254	32	1.00	4015	26	1.14 (0.68–1.92)	3722	23	1.45 (0.84–2.51)	0.193
Ischemic heart disease	5254	126	1.00	4015	91	0.98 (0.75–1.29)	3722	81	1.44 (1.08–1.91)	0.030
Cerebral hemorrhage	5254	24	1.00	4015	29	1.65 (0.96–2.84)	3722	27	2.21 (1.26–3.85)	0.005
Cerebral infarction	5254	100	1.00	4015	76	1.06 (0.78–1.43)	3722	65	1.26 (0.92–1.74)	0.170
Stroke	5254	121	1.00	4015	98	1.12 (0.86–1.47)	3722	79	1.28 (0.96–1.71)	0.094

*Adjusted for age group, sex, income, Charlson’s comorbidity score, area of residence, number of drugs taken, diabetes mellitus, dyslipidemia.