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# 고혈압환자에서 고혈압 약물 순응도가 심혈관 질환 사망 및 입원에 미치는 영향

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지도교수 조 비 룡

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

by

Soyeun Kim

A Thesis Submitted to the Department of Family Medicine in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in Medicine at the Seoul National University College of Medicine

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# Abstract

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

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**Objective**: The importance of adherence to antihypertensive treatments for the prevention of cardiovascular disease (CVD) has not been well elucidated. This study evaluated the effect of antihypertensive medication adherence on specific CVD mortality (ischemic heart disease [IHD], cerebral hemorrhage, and cerebral infarction).

**Methods**: 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 or older, were diagnosed with hypertension, and started newly prescribed antihypertensive medication in 2003 - 2004. Adherence to antihypertensive medication was estimated as the cumulative medication adherence (CMA). Subjects were divided into good (CMA

≥80%), intermediate (CMA 50 - 80%), and poor (CMA<50%) adherence groups. We used time-dependent Cox proportional hazards models to evaluate the association between medication adherence and health outcomes. The potential predictors of adherence to antihypertensive medication during first two year were evaluated through a multiple logistic regression model

**Results**: Patients with poor medication adherence had worse mortality from IHD (HR: 1.64, 95% CI: 1.16 - 2.31, P for trend=0.005), cerebral hemorrhage (H HR: 2.71, 95% CI: 1.65 - 4.47, P for trend<0.001), and heart failure (HR: 2.07, 95% CI: 1.05-6.74, P for trend=0.030) than those with good adherence. The estimated HRs of hospitalization for CVD were consistent with the mortality endpoint. High income level (OR: 0.82, 95% CI: 0.77 - 0.86), and taking multiple antihypertensive drug (OR: 0.86, 95% CI: 0.82 - 0.91), dyslipidemia (OR: 0.90, 95% CI: 0.83 - 0.96) were associated with good adherence to antihypertensive medication.

**Conclusions:** Poor medication adherence was associated with higher mortality and a greater risk of hospitalization for specific CVDs, emphasizing the importance of a monitoring system and strategies to improve medication adherence in clinical practice.

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**Keywords:** Cardiovascular outcomes, hospitalization, medication adherence, antihypertensive agent, stroke

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# Introduction

## 1. Hypertension and cardiovascular disease

Cardiovascular diseases (CVDs) are a leading cause of death in the world. Globally CVDs account for approximately 17.5 million deaths a year in 2012 (1). 7.4 million were due to ischemic heart disease and 6.7 million were due to strokes (2).

Hypertension is an important risk factor for coronary heart disease and stroke. The global prevalence of high blood pressure in adults aged 18 years and over was around 22% in 2014 (2). Because of population growth, ageing, behavioral and socioeconomic risk factors, the prevalence of people with raised blood pressure or uncontrolled hypertension rose from 600 million in 1980 to 1 billion in 2008 (3). High blood pressure contributes to about 54% of stroke and 47% of ischemic heart disease worldwide (4). Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke (3). Managing blood pressure in hypertensive patients is important for the prevention of CVD and the reduction of mortality (5, 6). The use of antihypertensive drug therapy reduces the risk of stroke by an estimated 34% and the risk of ischemic heart disease by 21% (7). A meta-analysis reported that blood pressure-lowering drugs reduce the risk of all CVD events by 24%, the risk of stroke by 21%, and the risk of CVD mortality by 19% compared with placebo (8).

## 2. Concept of medication adherence

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 (9). It includes the initiation of the treatment, implementation of the prescribed regimen, and discontinuation of the pharmacotherapy. Some studies classify adherence as either primary or secondary (10, 11). Primary nonadherence is the frequency with which patients fail to fill prescriptions when new medications are started so it is related to refilling and initiation of the medication therapy. Secondary nonadherence is defined as the medication being not taken as prescribed when prescriptions are filled.

Medication adherence is a growing concern to clinicians, healthcare systems because nonadherence is prevalent and associated with adverse health outcomes (12, 13) and higher costs of care (14, 15). Adherence rate to acute conditions are higher as compared with those to chronic diseases, however poor adherence rate is common for patients with chronic disease. Adherence to medication among patients with chronic diseases is suboptimal, dropping most dramatically during the first year after the start of therapy (12, 16). For example, half of the patients who are prescribed an antihypertensive drug will discontinue their medication within one year of starting the therapy (17-19). Mazzaglia et al found that 42.6% of patients were antihypertensive drug discontinuers and the severity of hypertension and high patients' comorbidity score were associated with the risk of discontinuation (hazard ratio [HR]: 1.30; 95% confidence interval[CI]:

1.18 - 1.30) (18). Patients with chronic diseases require a good partnership with their physician in order to achieve the long-term outcome goal.

### 3. Methods of assessing medication adherence

There are many diverse methods to assess medication adherence. The measurements of adherence were categorized as direct and indirect methods (9, 20). Direct methods include directly observed therapy, measurement of the drug or its metabolite in blood or urine, and evaluation of a biological marker in body fluids. Direct methods are objective and more accurate than indirect methods. For some drugs such as warfarin, valproate, lithium, the measure of concentration of drug is important to evaluate therapeutic level and use to evaluate medication adherence. However, there are also limitations to these direct methods. Using direct observation, patients can hide pill under tongue and discard them later. Measurements of biomarkers or metabolite are expensive for assay. Drug metabolism should be considered while using these methods. For instance, traces of neuroleptic and psychiatric medications can be detected in the blood even long after stopping the medication. Since individuals vary in physiological state and metabolic rate, drug plasma levels also differ after different individuals take the same dose of the same medicine. Furthermore, the concentration of serum drug can be affected variations in metabolism such as drug - drug interaction, and drug - food interaction. Although measuring these levels is a good and commonly used to assess medication adherence such as warfarin or

anti-epileptic drug, these direct methods are not practical for routine clinical use.

Indirect methods of adherence to medication include patient self-reports, patient questionnaires, patient diaries, pill counts, assessment of the patient's clinical response, rate of prescription refills, electronic medication monitors, and measurement of physiological markers (9). Patient questionnaires, self-reports are simple, inexpensive method. They can be administered as structured interviews, online assessments, written questionnaires, and voice response system. But these methods are susceptible to error with increases in time between visits and can be easily altered or biased by patients. The relatively poor sensitivity and specificity can occur due to false data input by patients, purposefully or accidently or faulty communication skills. Pill counts are the method to count the number of pills that remain in the patient's medication bottles or vials. Although this method is objective, quantifiable, and easy to perform, there are some limitations. The data can be manipulated by patients. This method cannot accurately capture the information on other aspects of taking medications, such as the exact timing of medication taking and drug holidays. Ascertaining rates of refilling prescriptions is one of the feasible and sustainable indirect methods (21). The use of pharmacy claims data to ascertain prescription refill is an accurate measure of overall adherence in a closed pharmacy system. A medical system that uses electronic medical records can provide the clinician or research scientist with available objective

information on refilling prescriptions that can be used to assess whether a patient is adhering to the regimen. Electronic pharmacy claim data facilitates an analysis of a large population and is one of the more frequently used indirect methods in the literature (22, 23). Adherence based on pharmacy refill data has been correlated with health outcome (24). However, this method correlates well with the quantity of doses taken but not the timing of the doses, and the assessment of adherence with these measures is more difficult when the length of follow-up varies between patients. Each direct and indirect approach has advantages and disadvantages. No method that is considered the gold standard. It depends on the clinical setting and availability of the data.

### 4. Adherence to antihypertensive medication and clinical outcomes

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 non-adherent (odds ratio [OR]: 3.44, 95% confidence interval [CI]: 1.60 - 7.37) (25). Another study showed that high adherence to antihypertensive medications was associated with higher odds (OR 1.45, 95% CI 1.04 - 2.02) of blood pressure control compared with those with medium or low levels of adherence (26).

Studies showed that patients with poor adherence to antihypertensive medication have a higher risk of adverse outcomes

(27, 28) and have higher health care costs (14) compared to patients with good adherence. Wu et al. conducted a retrospective cohort study using claims data from Taiwan's National Health Insurance (NHI) program. The study population consisted of 29,685 hypertensive patients, and the hospitalizations were ascertained from 1 January 2006 to 31 December 2006. Poor medication adherence significantly increased the risks of CVD hospitalization including ischemic heart disease, stroke, and other diseases of the circulatory system (OR: 1.43, 95% CI: 1.14 - 1.81) and all-cause hospitalization (OR: 1.47, 95% CI: 1.21 - 1.78) (28). A recent cohort study (29) reported that a good-adherence group had a significantly lower incidence of acute cardiovascular events, compared to a group with poor adherence to anti-hypertension medication (hazard ratio [HR]: 0.62, 95% CI: 0.40 - 0.96). Pittman et al. (30) also reported that patients with a medication adherence of 80% or higher decreased their risk of CVD-related hospitalization by 33% (OR: 1.33, 95% CI: 1.25 - 1.41) and emergency department visits by 45% (OR: 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 (31), while there has been no study of the association between medication adherence and specific CVD mortality.

## 5. Study for Korean population

Cardiovascular diseases (CVDs) are a second leading cause of death in Korea. 52.5 deaths per 100,000 persons were due to ischemic heart disease and 51.1 deaths per 100,000 persons were due to strokes

in 2012 (32). According to Korea National Health and Nutrition Examination Survey, the prevalence of hypertension in adults aged 30 years and over was around 32% in 2012 (33).

Only a few studies of antihypertensive medication adherence have been carried out in Korea. A study using claim data submitted to Korea's Health Insurance Review Agency showed that the overall cumulative medication adherence (CMA) of hypertensive patients was <60% and the good adherence rate (CMA≥80%) was <40% during the first year after starting the antihypertensive therapy (19). Medication adherence appeared 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 (19, 34, 35). In a cohort study using the Korean National Health Insurance Claims Database (KNHICD), non-adherence to antihypertensive therapy increased all-cause mortality and the risk of hospitalization for CVD (HR: 1.57, 95% CI: 1.40 - 1.76) (27). 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.

## 6. The aim of study

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. We hypothesized that poor adherence to antihypertensive medication would be associated

with increasing specific CVD mortality, all-cause mortality and hospitalization. We also conducted to identify affecting factors of antihypertensive medication adherence.

# Methods

## 1. 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.

In Korea, the Korea National Health Insurance (KNHI) program provides mandatory health insurance, offering coverage of medical care services to nearly 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 non-severe 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. Patients should visit a doctor to obtain a prescription and then visit a pharmacy to fill that prescription, according to the prescription-dispensation separation policy instituted in 2000. The KNHI pharmacy claims are generated when a patient uses insurance coverage to fill a prescription. The claims are then entered into the KNHI's claims database.

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 regarding the inpatient or outpatient services an individual receives, such as diagnosis information classified by the International Classification of Diseases, 10th 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.

## 2. Study subjects

We defined the study population as subjects who were aged 20 years or older, 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 (Anatomical Therapeutic Chemical [ATC] classification code C08, diuretics [ATC code C03], angiotensin-converting enzyme inhibitors [ATC code C09], angiotensin receptor blockers [ATC code C09], beta-blockers [ATC code C07], or other antihypertensive drugs [ATC code C02] in 2003 - 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 ischemic heart diseases (ICD-10: I20 to I25), cerebrovascular diseases

(ICD-10: I60 to I64, I67, I69), or heart failure (ICD-10: I50) before 2003.

Based on 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 two year were included, because CMA can only be calculated when patients have multiple prescriptions filled. Based on these criteria, 34,716 patients were finally selected for the analyses (Figure1). 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).

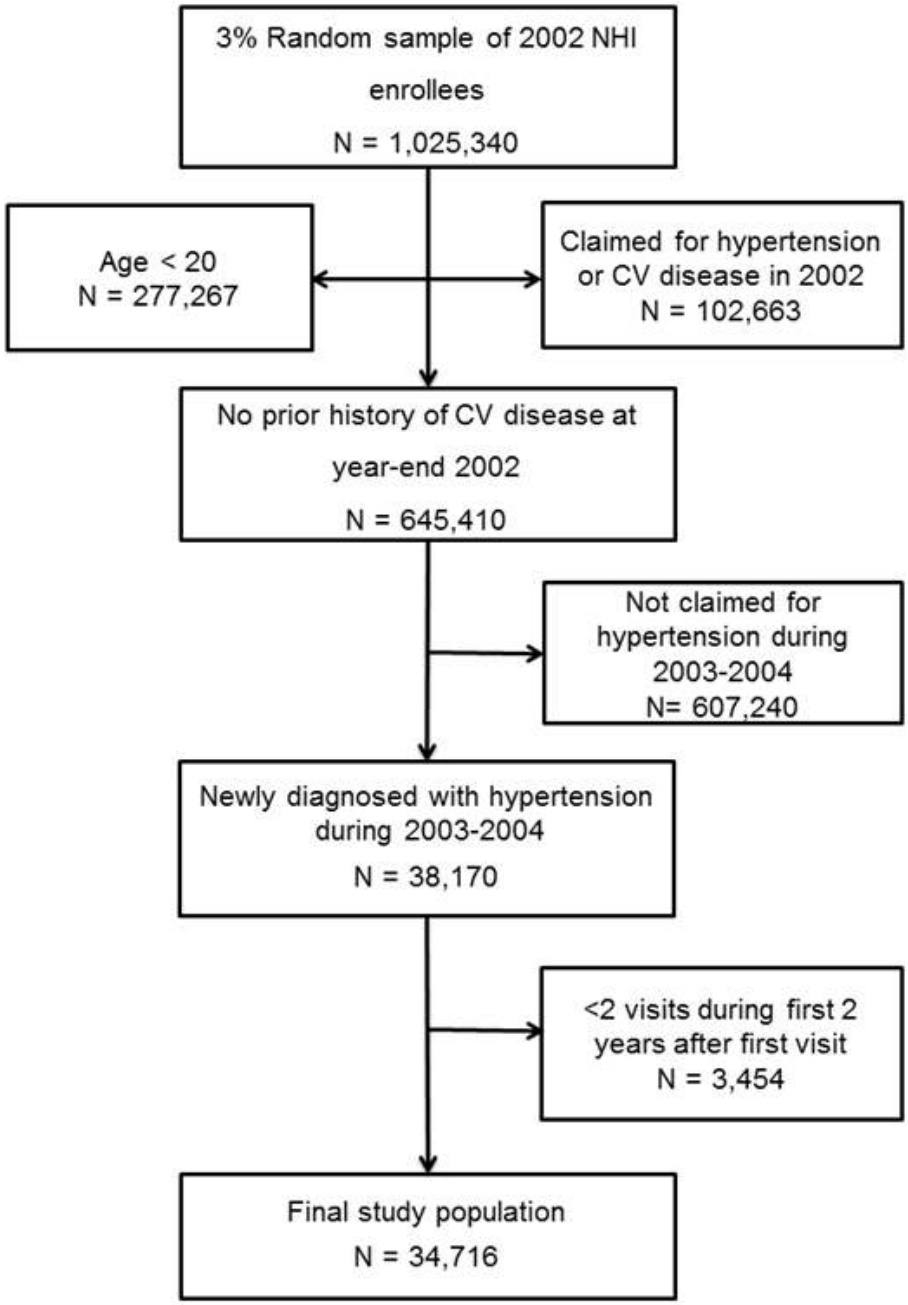


Figure 1. Flow chart showing inclusion and exclusion criteria for the selected study population

### 3. Assessment of adherence

Adherence to a medication was assessed using the CMA scale, based on pharmacy claims data (23, 36, 37). 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 (23, 34, 36). Calculation example was shown in Figure 2. Pills from the last prescriptions were not included because their consumption was unknown (22). The 80% cutoff was previously used in related studies (19, 34, 38). We defined the above 80% of CMA as adherence and the below 80% of CMA as nonadherence. For analytical purposes, we further classified drug adherence into three groups according to CMA level: good (CMA≥80%), intermediate (50% ≤CMA < 80%), and poor (CMA<50%).

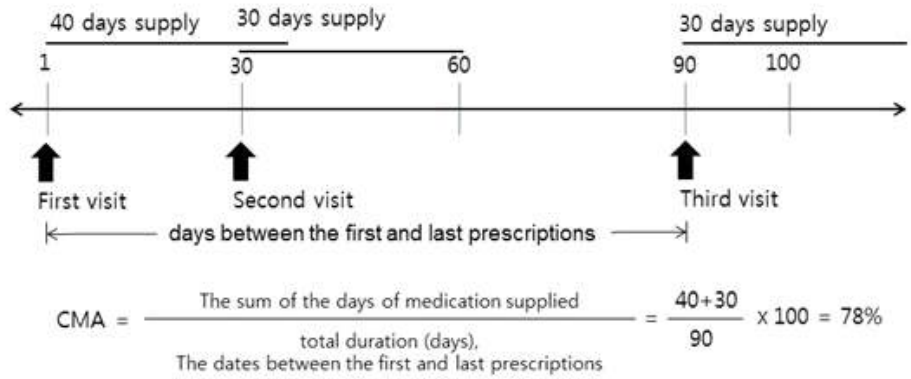


Figure 2. The cumulative medication adherence (CMA) calculation

## 4. Outcomes

CVD was defined as a composite endpoint of acute myocardial infarction (AMI, ICD-10: I21 to I23) and other IHD, including angina pectoris (ICD-10: I20, I24, I25), or cerebrovascular events, such as cerebral hemorrhage (ICD-10: I60 to I62), cerebral infarction (ICD-10: I63), and other stroke (ICD-10: I64, I67, I69). IHD was defined as a composite endpoint of AMI and other IHD (ICD-10: I20-25). Stroke was defined as all cerebrovascular events (ICD-0: I60 to I64, I67, 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. Third outcome of study was factors affecting adherence to antihypertensive medication.

## 5. Statistical analysis

The baseline characteristics of hypertensive patients according to their first 2years' 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. In order 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 long-term cumulative effect of blood pressure control (39), 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 (CMA≥80% was regarded as the reference value). All multivariate models were adjusted for age, sex, income level, residential regions, diabetes mellitus, dyslipidemia, Charlson's comorbidity score (40), and the number of antihypertensive medications included in the first prescription at the index date. Patients who were diagnosed with diabetes or dyslipidemia and were prescribed antihyperglycemic or antihyperlipidemic medication within the past year from the index date were defined as having diabetes or dyslipidemia. The information about diabetes, dyslipidemia, and Charlson's comorbidity score were assessed for the period between

the dates 1 year prior to the index date and the end of the study period.

To verify the robustness of our findings, sensitivity analyses were performed. We performed time-dependent Cox proportional hazards models with subset which excluded patient who died within 2 years after the first visit (N=33,728) in order to ensure a sufficient observation time interval for adherence assessment. We calculated HRs of subset who died within 2 years after the first visit (N=988) to evaluate the association between medication adherence and CVD mortality or hospitalization. We performed time-dependent Cox proportional hazards models to evaluate association between adherence to antihypertensive medication and non-CVD mortality or non-CVD hospitalization. We performed additional analysis with the subset which never been hospitalized for non-cardiovascular disease during study period (N=12991, 38.5%) to consider the effects of changes in medication adherence for non-CVD hospitalization.

The potential predictors of adherence to antihypertensive medication during first two year were evaluated through a multiple logistic regression model and reported as OR and 95% CIs.

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

# Results

## 1. Subject characteristics

Of the 34716 subjects included in the study, 16,275 were men and 18,441 women. Among these, 3929 (11.3%) died during follow up after the date when they received their first prescription for antihypertensive agents. Subjects were classified according to their CMA level as 12,647 (36.4%) good, 10,846 (31.2%) intermediate, and 11,223 (32.4%) poor adherence.

Table 1 shows the baseline characteristics of the hypertensive patients according to medication adherence in the first 2years. At baseline, the median CMAs were 91% in good, 67% in intermediate, and 28% in poor adherence group, respectively. More than 70% of patients were aged 50 years or older and 53% were women. The majority of patients lived in a metropolitan or city area. More than 60% of the study subjects did not have any disease comorbidities (63.2%), while 33% had diabetes. Calcium channel blockers (38.2%) were the most commonly prescribed first antihypertensive medications, followed by beta-blockers (15.4%), diuretics (14.8%), angiotensin-converting enzyme inhibitors (10.0%), and angiotensin receptor blockers (9.4%).

Table 1. Characteristics of the study population (N=34,716)

| Characteristics | N | % |
|---|---|---|
| Sex | | |
| Men | 16275 | 46.9 |
| Women | 18441 | 53.1 |
| Age (years) | | |
| <50 | 9554 | 27.5 |
| 50 - 59 | 8811 | 25.4 |
| 60 - 69 | 10060 | 29.0 |
| ≥70 | 6291 | 18.1 |
| Income level | | |
| Low | 13359 | 38.5 |
| Middle | 10814 | 31.1 |
| High | 10543 | 30.4 |
| Residence | | |
| Metropolitan | 15342 | 44.2 |
| City | 13951 | 40.2 |
| Rural | 5423 | 15.6 |
| Type of insurance | | |
| Medicare | 34369 | 99.0 |
| Medicaid | 347 | 1.0 |
| Charlson's comorbidity score | | |
| 0 | 21833 | 62.9 |
| 1 | 7836 | 22.6 |
| 2 | 3292 | 9.5 |
| ≥3 | 1755 | 5.0 |
| Diabetes mellitus | | |
| No | 23079 | 66.5 |
| Yes | 11637 | 33.5 |

| | | |
|---|---|---|
| Dyslipidemia | | |
| No | 30932 | 89.1 |
| Yes | 3784 | 10.9 |
| No. of antihypertensive medications taken | | |
| 1 | 13574 | 39.1 |
| 2 | 12766 | 36.8 |
| ≥3 | 8376 | 24.1 |
| Prescribed antihypertensive medication | | |
| CCB | 13275 | 38.2 |
| Beta blocker | 5359 | 15.4 |
| Diuretics | 5128 | 14.8 |
| ACEI | 3470 | 10.0 |
| ARB | 3262 | 9.4 |
| Cumulative medication adherence | | |
| Good | 12647 | 36.4 |
| Median, IQR | 0.91 | 0.86,0.97 |
| Intermediate | 10846 | 31.2 |
| Median, IQR | 0.67 | 0.59,0.74 |
| Poor | 11223 | 32.4 |
| Median, IQR | 0.28 | 0.14, 0.41 |

CCB - Calcium channel blockers; ACEI - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blockers; IQR - interquartile range

## 2. Adherence to antihypertensive medications and CVD mortality

The mortality of CVD and all-cause mortality were inversely associated with antihypertensive medication adherence (Table 2). This correlation remained robust even after adjustment for covariates, taking into account the potential confounders in the multivariate model. The risk in poor adherent patients was higher than the risk in good adherence patients for both all-cause mortality (HR: 1.69, 95% CI: 1.53 - 1.86), the mortality of stroke (HR: 1.77, 95% CI: 1.37 - 2.27) and IHD (HR: 1.49, 95% CI: 1.09 - 2.04). The mortality risk of cerebral hemorrhage in poor adherence group was 2.71-fold higher (HR: 2.71, 95% CI: 1.65 - 4.47) than the risk in good adherence group.

Of the subset which excluded patient who died within 2 years after the first visit (N=33,728), CVD- and all-cause mortality were correlated with poor medication adherence by three levels of CMA (good, intermediate, poor), as shown by the P-for-trend values. The risk of stroke mortality increased with decreasing medication adherence (intermediate: HR: 1.68, 95% CI: 1.30 - 2.18; poor: HR: 1.92, 95% CI: 1.47 - 2.50; P for trend<0.001). The mortality risks of the individual endpoints, including cerebral hemorrhage, cerebral infarction, and IHD were also increased, similarly to the outcome of all-cause mortality. (Table 3)

The results for subset who died within 2 years after the first visit (N=988) were shown in Table 4. There were not significant associations between antihypertensive medication adherence and CVD mortality (Table 4).

The risk of heart failure mortality in poor adherence group was 2.07 fold high than the mortality risk in good adherence group (intermediate: HR: 2.65, 95% CI: 1.16 - 6.02; poor: HR: 2.07, 95% CI: 1.05 - 6.74) (Table 5). The cancer mortality risk was not associated with antihypertensive medication adherence However, the risk of non-CVD mortality and non-disease mortality (accidents) were also increased, similarly to the outcome of all-cause mortality (Table 5, 6).

Table 2. The risk of all-cause death, and cardiovascular disease mortality by antihypertensive medication adherence (N=34,716)

| 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 | 12647 | 886 | 1.00 | 10846 | 1010 | 1.29 (1.18 - 1.41) | 11223 | 931 | 1.69 (1.53 - 1.86) | <0.001 |
| All-CVD mortality | 12647 | 210 | 1.00 | 10846 | 219 | 1.18 (0.98-1.43) | 11223 | 218 | 1.65 (1.36-2.01) | <0.001 |
| Stroke | 12647 | 122 | 1.00 | 10846 | 148 | 1.36 (1.07 - 1.74) | 11223 | 142 | 1.77 (1.37 - 2.27) | <0.001 |
| Cerebral hemorrhage | 12647 | 27 | 1.00 | 10846 | 27 | 1.18 (0.69 - 2.01) | 11223 | 42 | 2.71 (1.65 - 4.47) | <0.001 |
| Cerebral infarction | 12647 | 50 | 1.00 | 10846 | 62 | 1.39 (0.95 - 2.02) | 11223 | 48 | 1.33 (0.89 - 2.00) | 0.144 |
| Other stroke | 12647 | 45 | 1.00 | 10846 | 59 | 1.43 (0.97-2.11) | 11223 | 52 | 1.72 (1.16-2.64) | 0.007 |
| Ischemic heart disease | 12647 | 88 | 1.00 | 10846 | 71 | 0.93 (0.68 - 1.27) | 11223 | 76 | 1.49 (1.09 - 2.04) | 0.023 |
| Acute myocardial infarction | 12647 | 69 | 1.00 | 108468 | 47 | 0.79 (0.55 - 1.15) | 11223 | 50 | 1.26 (0.87 - 1.84) | 0.339 |

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

Table 3.The risk of all-cause death, and cardiovascular disease mortality by antihypertensive medication adherence with the subset which excluded patient who died within 2 years after the first visit (N=33,728)

| Outcome | Good adherence | | | Intermediate adherence | | | Poor adherence | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) |
| All-cause mortality | 12316 | 742 | 1.00 | 10568 | 897 | 1.39 (1.26 - 1.53) | 10844 | 880 | 1.75 (1.58 - 1.93) |
| All-CVD mortality | 12316 | 164 | 1.00 | 10568 | 209 | 1.46 (1.19-1.79) | 10844 | 208 | 1.81 (1.47-2.24) |
| Stroke | 12316 | 99 | 1.00 | 10568 | 145 | 1.68 (1.30 - 2.18) | 10844 | 135 | 1.92 (1.47 - 2.50) |
| Cerebral hemorrhage | 12316 | 23 | 1.00 | 10568 | 27 | 1.35 (0.77 - 2.35) | 10844 | 34 | 2.19 (1.28 - 3.77) |
| Cerebral infarction | 12316 | 34 | 1.00 | 10568 | 57 | 1.49 (0.95 - 2.35) | 10844 | 45 | 1.92 (1.25 - 2.96) |
| Other stroke | 12316 | 44 | 1.00 | 10568 | 63 | 1.63 (1.10-2.40) | 10844 | 55 | 1.72 (1.15-2.58) |
| Ischemic heart disease | 12316 | 65 | 1.00 | 10568 | 64 | 1.11 (0.78 - 1.57) | 10844 | 73 | 1.64 (1.16 - 2.31) |
| Acute myocardial infarction | 12316 | 50 | 1.00 | 10568 | 45 | 1.02 (0.68 - 1.53) | 10844 | 45 | 1.32 (0.87 - 1.99) |

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

Table 4. The risk of all-cause death, and cardiovascular disease mortality by antihypertensive medication adherence with subset who died within 2 years after the first visit (N=988)

| 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 | 314 | 310 | 1.00 | 288 | 286 | 0.81 (0.69 - 0.96) | 386 | 385 | 0.75 (0.65 - 0.88) | <0.001 |
| All-CVD mortality | 314 | 80 | 1.00 | 288 | 61 | 0.84 (0.60-1.18) | 386 | 91 | 0.95 (0.70-1.28) | 0.751 |
| Stroke | 314 | 50 | 1.00 | 288 | 48 | 1.08 (0.72 - 1.61) | 386 | 64 | 1.11 (0.77 - 1.62) | 0.575 |
| Cerebral hemorrhage | 314 | 10 | 1.00 | 288 | 9 | 1.00 (0.41 - 2.48) | 386 | 20 | 1.80 (0.83 - 3.88) | 0.113 |
| Cerebral infarction | 314 | 24 | 1.00 | 288 | 20 | 0.93 (0.51 - 1.69) | 386 | 28 | 0.95 (0.55 - 1.66) | 0.875 |
| Other stroke | 314 | 16 | 1.00 | 288 | 19 | 1.41 (0.72-2.76) | 386 | 16 | 0.98 (0.48-1.98) | 0.939 |
| Ischemic heart disease | 314 | 30 | 1.00 | 288 | 13 | 0.50 (0.26 - 0.97) | 386 | 27 | 1.49 (0.44 - 1.27) | 0.299 |
| Acute myocardial infarction | 314 | 22 | 1.00 | 288 | 10 | 0.54 (0.25 - 1.15) | 386 | 17 | 0.65 (0.34 - 1.23) | 0.183 |

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

Table 5. The risk of non-CVD mortality by antihypertensive medication adherence (N=34,716)

| Outcome | Good adherence | | | Intermediate adherence | | | Poor adherence | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) |
| Non-CVD mortality | 12647 | 677 | 1.00 | 10846 | 792 | 1.32 (1.19-1.46) | 11223 | 714 | 1.69 (1.51-1.88) |
| Heart failure | 12647 | 8 | 1.00 | 10846 | 21 | 2.65 (1.16-6.02) | 11223 | 11 | 2.07 (1.05-6.74) |
| Non-disease mortality | 12647 | 82 | 1.00 | 10846 | 89 | 1.24 (0.91-1.67) | 11223 | 94 | 1.91 (1.41-2.59) |
| All-cancer | 12647 | 271 | 1.00 | 10846 | 290 | 1.25 (1.06-1.48) | 11223 | 199 | 1.25 (1.03-1.51) |
| Stomach cancer | 12647 | 30 | 1.00 | 10846 | 46 | 1.80 (1.13-2.87) | 11223 | 25 | 1.42 (0.86-2.46) |
| Colon cancer | 12647 | 32 | 1.00 | 10846 | 23 | 0.82 (0.48-1.40) | 11223 | 20 | 1.12 (0.63-1.99) |
| Liver cancer | 12647 | 38 | 1.00 | 10846 | 39 | 1.17 (0.75-1.84) | 11223 | 32 | 1.42 (0.87-2.30) |
| Lung cancer | 12647 | 69 | 1.00 | 10846 | 79 | 1.38 (1.00-1.91) | 11223 | 51 | 1.46 (0.84-1.77) |

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

Table 6. The risk of non-CVD mortality by antihypertensive medication adherence with the subset which excluded patient who died within 2 years after the first visit (N=33,728)

| 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) | |
| Non-CVD mortality | 12316 | 577 | 1.00 | 10568 | 693 | 1.37 (1.22-1.53) | 10844 | 668 | 1.69 (1.51-1.90) | <0.001 |
| Heart failure | 12316 | 15 | 1.00 | 10568 | 12 | 0.82 (0.38-1.77) | 10844 | 17 | 1.63 (0.79-3.33) | 0.200 |
| Non-disease mortality | 12316 | 53 | 1.00 | 10568 | 76 | 1.63 (1.15-2.32) | 10844 | 75 | 2.12 (1.48-3.04) | <0.01 |
| All-cancer | 12316 | 247 | 1.00 | 10568 | 253 | 1.20 (1.00-1.42) | 10844 | 181 | 1.13 (0.93-1.37) | 0.166 |
| Stomach cancer | 12316 | 37 | 1.00 | 10568 | 38 | 1.20 (0.76-1.89) | 10844 | 20 | 0.84 (0.48-1.47) | 0.685 |
| Colon cancer | 12316 | 31 | 1.00 | 10568 | 27 | 1.00 (0.60-1.69) | 10844 | 17 | 0.84 (0.46-1.53) | 0.690 |
| Liver cancer | 12316 | 38 | 1.00 | 10568 | 28 | 0.84 (0.52-1.38) | 10844 | 26 | 1.02 (0.61-1.71) | 0.769 |
| Lung cancer | 12316 | 52 | 1.00 | 10568 | 64 | 1.47 (1.02-2.12) | 10844 | 53 | 1.46 (0.99-2.17) | 0.048 |

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

### 3. 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 by three levels of CMA, as shown by the P for trend values (Table 7).The hospitalization risk in poor adherence patients was higher than the risk in good adherent patients for cerebral hemorrhage (intermediate: HR: 1.66, 95% CI: 1.30 - 2.12; poor: HR: 2.55, 95% CI: 1.98 - 3.27; P for trend<0.001), cerebral infarction (intermediate: HR: 1.37, 95% CI: 1.22 - 1.54; poor: HR: 1.72, 95% CI: 1.51 - 1.94; P for trend<0.001), and IHD (intermediate: HR: 1.19, 95% CI: 1.08 - 1.32; poor: HR: 1.58, 95% CI: 1.42 - 1.77; P for trend<0.001).

The hospitalizations for specific CVD were inversely associated with antihypertensive medication adherence by CMA in the subset (N=33,728) which excluded patient who died within 2 years after the first visit (Table 8). The HRs for the risk of hospitalization for cerebral hemorrhage were estimated as 1.25 (95% CI: 0.94 - 1.67) for the intermediate adherence group, and 1.90 (95% CI: 1.42 - 2.53) for the poor adherence group (P for trend<0.001).

The results for subset who died within 2 years after the first visit (N=988) were shown in Table 9. The risk of hospitalization for stroke increased stepwise with decreasing adherence by CMA, as shown by the P for trend values (intermediate: HR: 1.06, 95% CI: 0.64 - 1.75; poor: HR: 1.60, 95% CI: 1.03 - 2.48; P for trend=0.025). There were not significant associations between antihypertensive medication

adherence and CVD mortality except stroke (Table 9).

The HRs for the risk of hospitalization for Heart failure was estimated as 2.37 (95%CI: 1.87 - 3.00) in poor adherence group (Table 10). The risk of hospitalization for heart failure increased with decreasing adherence (intermediate: HR: 52, 95% CI: 1.21 - 1.93; poor: HR: 2.37, 95% CI: 1.87 - 3.00; P for trend<0.001). The risk of hospitalization for cancer was not associated with antihypertensive medication adherence (Table 10, 11).

Table 7. The risk of hospitalization for cardiovascular disease by antihypertensive medication adherence (N=34,716)

| Outcome | Good adherence | | | Intermediate adherence | | | Poor adherence | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) |
| All-CVD hospitalization | 12647 | 1266 | 1.00 | 10846 | 1376 | 1.28 (1.18 - 1.38) | 11223 | 1199 | 1.69 (1.56 - 1.83) |
| Stroke | 12647 | 608 | 1.00 | 10846 | 738 | 1.39 (1.25 - 1.55) | 11223 | 651 | 1.83 (1.64 - 2.05) |
| Cerebral hemorrhage | 12647 | 110 | 1.00 | 10846 | 159 | 1.66 (1.30 - 2.12) | 11223 | 157 | 2.55 (1.98 - 3.27) |
| Cerebral infarction | 12647 | 516 | 1.00 | 10846 | 619 | 1.37 (1.22 - 1.54) | 11223 | 523 | 1.72 (1.51 - 1.94) |
| Other stroke | 12647 | 26 | 1.00 | 10846 | 40 | 1.73 (1.05 - 2.84) | 11223 | 33 | 2.18 (1.29 - 3.70) |
| Ischemic heart disease | 12647 | 737 | 1.00 | 10846 | 756 | 1.19 (1.08 - 1.32) | 11223 | 654 | 1.58 (1.42 - 1.77) |
| Acute myocardial infarction | 12647 | 147 | 1.00 | 10846 | 159 | 1.25 (1.00 - 1.57) | 11223 | 171 | 1.98 (1.58 - 2.49) |

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

Table 8.The risk of hospitalization for cardiovascular disease by antihypertensive medication adherence with the subset which excluded patient who died within 2 years after the first visit (N=33,728)

| 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-CVD hospitalization | 12316 | 886 | 1.00 | 10568 | 808 | 1.07 (0.97 - 1.18) | 10844 | 757 | 1.41 (1.28 - 1.56) | <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 |
| 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 |
| Other stroke | 12316 | 33 | 1.00 | 10568 | 23 | 0.76 (0.45 - 1.30) | 10844 | 25 | 1.02 (0.60 - 1.74) | 0.974 |
| 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 |
| 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 |

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

Table 9.The risk of hospitalization for cardiovascular disease by antihypertensive medication adherence with subset who died within 2 years after the first visit (N=988)

| Outcome | Good adherence | | | Intermediate adherence | | | Poor adherence | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) |
| All-CVD hospitalization | 314 | 48 | 1.00 | 288 | 43 | 0.94 (0.62 - 1.43) | 386 | 85 | 1.41 (0.99 - 2.02) |
| Stroke | 314 | 31 | 1.00 | 288 | 31 | 1.06 (0.64 - 1.75) | 386 | 63 | 1.60 (1.03 - 2.48) |
| Cerebral hemorrhage | 314 | 10 | 1.00 | 288 | 10 | 1.06 (0.44 - 2.57) | 386 | 18 | 1.55 (0.70 - 3.43) |
| Cerebral infarction | 314 | 20 | 1.00 | 288 | 22 | 1.18 (0.64 - 2.17) | 386 | 45 | 1.75 (1.02 - 2.99) |
| Other stroke | 314 | 2 | 1.00 | 288 | 3 | 1.90 (0.30 - 11.80) | 386 | 3 | 1.49 (0.24 - 9.44) |
| Ischemic heart disease | 314 | 19 | 1.00 | 288 | 15 | 0.87 (0.44 - 1.73) | 386 | 29 | 1.25 (0.70 - 2.25) |
| Acute myocardial infarction | 314 | 14 | 1.00 | 288 | 7 | 0.53 (0.21 - 1.33) | 386 | 13 | 0.71 (0.33 - 1.53) |

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

Table 10. The risk of hospitalization for non-CVD disease by antihypertensive medication adherence (N=34,716)

| 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) | |
| Non-CVD hospitalization | 12647 | 5949 | 1.00 | 10846 | 5702 | 1.15 (1.11 - 1.20) | 11223 | 4012 | 1.25 (1.20 - 1.30) | <0.001 |
| Heart failure | 12647 | 121 | 1.00 | 10846 | 175 | 1.52 (1.21 - 1.93) | 11223 | 183 | 2.37 (1.87 - 3.00) | <0.001 |
| All-cancer | 12647 | 794 | 1.00 | 10846 | 755 | 1.12 (1.02 - 1.24) | 11223 | 453 | 1.07 (0.95 - 1.20) | 0.153 |
| Stomach cancer | 12647 | 129 | 1.00 | 10846 | 144 | 1.38 (1.09 - 1.76) | 11223 | 83 | 1.30 (0.98 - 1.72) | 0.031 |
| Colon cancer | 12647 | 131 | 1.00 | 10846 | 121 | 1.10 (0.86 - 1.41) | 11223 | 56 | 0.81 (0.59 - 1.12) | 0.360 |
| Liver cancer | 12647 | 81 | 1.00 | 10846 | 81 | 1.16 (0.85 - 1.58) | 11223 | 49 | 1.07 (0.74 - 1.54) | 0.602 |
| Lung cancer | 12647 | 124 | 1.00 | 10846 | 140 | 1.34 (1.05 - 1.71) | 11223 | 78 | 1.01 (0.76 - 1.36) | 0.630 |

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

Table 11. The risk of hospitalization for non-CVD disease by antihypertensive medication adherence with the subset which excluded patient who died within 2 years after the first visit (N=33,728)

| Outcome | Good adherence | | | Intermediate adherence | | | Poor adherence | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) |
| Non-CVD hospitalization | 12316 | 3845 | 1.00 | 10568 | 3448 | 1.10 (1.05 - 1.16) | 10844 | 2387 | 1.09 (1.03 - 1.15) |
| Heart failure | 12316 | 104 | 1.00 | 10568 | 126 | 1.29 (0.99 - 1.67) | 10844 | 108 | 1.44 (1.09 - 1.90) |
| All-cancer | 12316 | 586 | 1.00 | 10568 | 513 | 1.03 (0.91 - 1.15) | 10844 | 334 | 0.95 (0.83 - 1.09) |
| Stomach cancer | 12316 | 101 | 1.00 | 10568 | 103 | 1.23 (0.93 - 1.62) | 10844 | 59 | 1.00 (0.72 - 1.39) |
| Colon cancer | 12316 | 105 | 1.00 | 10568 | 82 | 0.92 (0.69 - 1.23) | 10844 | 54 | 0.84 (0.60 - 1.17) |
| Liver cancer | 12316 | 64 | 1.00 | 10568 | 51 | 0.92 (0.63 - 1.33) | 10844 | 33 | 0.78 (0.51 - 1.20) |
| Lung cancer | 12316 | 81 | 1.00 | 10568 | 84 | 1.23 (0.91 - 1.67) | 10844 | 66 | 1.22 (0.88 - 1.71) |

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

### 4. Adherence to antihypertensive medications and CVD outcomes in non-CVD hospitalization subset (N=12991)

Among non-hospitalization subset (N=12991, 38.5%), poor medication adherence was associated with higher all-cause mortality (intermediate: HR: 1.47, 95% CI: 1.16 - 2.86; 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; poor: HR: 1.65, 95% CI: 1.11 - 2.46; P for trend: 0.013) (Table 12).

Among non-hospitalization subset (N=12991, 38.5%), though the trend was not statistically significant, the risk of hospitalization for CVD increased with decreasing adherence (Table 13).

Table 12. Association between antihypertensive medication adherence and mortality of CVD, or all-cause death with the subset which never been hospitalized for non-CVD 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 |
| Stroke | 5254 | 35 | 1.00 | 4015 | 31 | 1.29 (0.79 - 2.09) | 3722 | 31 | 1.51 (0.92 - 2.48) | 0.097 |
| 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 |
| Other stroke | 5254 | 14 | 1.00 | 4015 | 16 | 1.70 (0.83 - 3.51) | 3722 | 10 | 1.18 (0.51 - 2.69) | 0.571 |
| 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 |
| Acute myocardial infarction | 5254 | 14 | 1.00 | 4015 | 16 | 1.59 (0.77 - 3.27) | 3722 | 13 | 1.70 (0.80 - 3.77) | 0.144 |

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

Table 13. Association between antihypertensive medication adherence and hospitalization for CVD in the subset which never been hospitalized for non-CVD during study period (N=12991)

| Outcome | Good adherence | | | Intermediate adherence | | | Poor adherence | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) | Cohort N | Cases N | HR (95%CI) |
| All-CVD hospitalization | 5254 | 140 | 1.00 | 4015 | 107 | 1.09 (0.85-1.41) | 3722 | 98 | 1.42 (1.09-1.85) |
| Stroke | 5254 | 121 | 1.00 | 4015 | 98 | 1.12 (0.86 - 1.47) | 3722 | 79 | 1.28 (0.96 - 1.71) |
| Cerebral hemorrhage | 5254 | 24 | 1.00 | 4015 | 29 | 1.65 (0.96 - 2.84) | 3722 | 27 | 2.21 (1.26 - 3.85) |
| Cerebral infarction | 5254 | 100 | 1.00 | 4015 | 76 | 1.06 (0.78 - 1.43) | 3722 | 65 | 1.26 (0.92 - 1.74) |
| Ischemic heart disease | 5254 | 126 | 1.00 | 4015 | 91 | 0.98 (0.75 - 1.29) | 3722 | 81 | 1.44 (1.08 - 1.91) |
| Acute myocardial infarction | 5254 | 32 | 1.00 | 4015 | 26 | 1.14 (0.68 - 1.92) | 3722 | 23 | 1.45 (0.84 - 2.51) |

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

### 5. Factors affecting adherence to antihypertensive medication

We analyzed the factors affecting nonadherence to antihypertensive medications using a multiple logistic regression model. The risk of nonadherence was relatively high in patients who were women, Younger age (age<50) and low income level. Medication nonadherence was correlated with increasing a Charlson's comorbidity score. Rural residential area was associated with lower rate of good medication adherence. Rate of medication nonadherence increased from metropolitan city to city (OR: 1.12, 95% CI: 1.07 - 1.18), via rural area (OR: 1.44, 95% CI: 1.34 - 1.54). Patients taking more than two different classes of antihypertensive medications had a lower risk of nonadherence than patients taking one class of antihypertensive medication (OR: 0.86, 95% CI: 0.82 - 0.91). The risk of nonadherence was relatively low in patients who take a angiotensin receptor blockers (OR: 0.88, 95% CI: 0.81 - 0.95)

Table 14. Factors affecting nonadherence to antihypertensive medication

| | Odds ratio | 95% confidence interval |
|---|---|---|
| Sex | | |
| Men | 1.00 | |
| Women | 1.15 | 1.10-1.20 |
| Age | | |
| <50 | 1.00 | |
| 50-59 | 0.75 | 0.70- 0.79 |
| 60-69 | 0.75 | 0.71-0.81 |
| ≥70 | 0.92 | 0.85-0.99 |
| Income level | | |
| Low | 1.00 | |
| Middle | 0.95 | 0.90- 1.01 |
| High | 0.82 | 0.77-0.86 |
| Residence | | |
| Metropolitan | 1.00 | |
| City | 1.12 | 1.07-1.18 |
| Rural | 1.44 | 1.34-1.54 |
| Type of insurance | | |
| Medicare | 1.00 | |
| Medicaid | 1.11 | 0.88- 1.41 |
| Charlson's comorbidity score | | |
| 0 | 1.00 | |
| 1 | 1.25 | 1.18-1.32 |
| 2 | 1.43 | 1.31-1.55 |
| ≥3 | 1.68 | 1.50-1.88 |
| Prevalence of diabetes mellitus | | |
| No | 1.00 | |
| Yes | 1.01 | 0.96-1.07 |
| Prevalence of dyslipidemia | | |
| No | 1.00 | |
| Yes | 0.90 | 0.83-0.96 |
| No. of AHT classes | | |
| 1 | 1.00 | |
| 2 | 0.86 | 0.82-0.91 |

| | | |
|---|---|---|
| ≥3 | 0.87 | 0.82-0.93 |
| First prescription | | |
| Calcium channel blocker | 1.00 | |
| Beta blocker | 0.99 | 0.92-1.05 |
| Diuretics | 1.05 | 0.98-1.13 |
| ACEI | 1.02 | 0.94-1.09 |
| ARB | 0.89 | 0.82-0.97 |

# Discussion

The present 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 (18% higher risk) to poor adherence (65% higher risk). The trend of increasing risk across the adherence groups was statistically significant (P-for-trend values of the HRs for cerebral hemorrhage, and ischemic heart disease 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 2.19 fold higher risk, P for trend<0.001). The risk of heart failure mortality increased with decreasing medication adherence (intermediate: HR: 2.65, 95% CI: 1.16 - 6.02; poor: HR: 2.07, 95% CI: 1.05 - 6.74; P for trend<0.030). The results in the subset which excluded patient who died within 2 years after the first visit (N=33,728) were similar to the mortality and hospitalization risk in total study population. We analyzed the associations of between adherence to antihypertensive medication and

CVD outcomes in the subset which never been hospitalized for non-cardiovascular disease during study period (N=12991, 38.5%) to consider the effects of changes in medication adherence for non-CVD hospitalization. Among non-hospitalization subset, poor medication adherence was associated with higher all-cause mortality and all-CVD mortality. Though this trend was not statistically significant, the risk of hospitalization for CVD increased with decreasing adherence. Subset analysis provides further support for our finding regarding 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 (6, 7, 41, 42), 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 (29, 43, 44), reflecting the importance of maintaining optimal medication adherence. Ho et al. (24) evaluated the association between mortality and medication adherence among patients with coronary artery disease. They showed that antihypertensive medication nonadherence increased both the risk of CVD mortality (beta-blockers: HR: 1.53, 95% CI: 1.16 - 2.01, angiotensin-converting enzyme inhibitors: HR: 1.66, 95% CI: 1.26 - 2.20) and the risk of all-cause mortality (beta-blockers: HR: 1.50, 95% CI: 1.33-1.71, angiotensin-converting enzyme inhibitors: HR: 1.74, 95% CI: 1.52-1.98). Our study demonstrated an association between

adherence to antihypertensive medication and disease-specific mortality (IHD, cerebral hemorrhage, cerebral infarction) as well as all-cause mortality. The correlation of low adherence to antihypertensive medication on cerebral hemorrhage mortality (poor adherence HR: 2.71, 95% CI: 1.65 - 4.47, P for trend<0.001) was greater than that on IHD mortality (poor adherence HR: 1.49, 95% CI: 1.09 - 2.04, P for trend=0.023). This is an original finding of the present 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 (27, 28, 45) regarding the association of adherence to antihypertensive medication on hospitalization for CVD. Compared with those patients with good medication adherence, patients with poor adherence were 1.98 times more likely to require hospitalization for AMI. The risk of hospitalization for cerebral hemorrhage increased more prominently than that for AMI or cerebral infarction. The results of this study are consistent with those of prior studies (46, 47). Kettani et al. reported that high adherence to antihypertensive medication significantly decreased the risk of cerebrovascular disease (RR: 0.78, 95% CI: 0.70 - 0.87), compared with lower adherence. Nonadherence in newly diagnosed hypertensive patients has been reported to increase the risk of hospitalization for coronary disease by 13%, the risk of hospitalization for acute myocardial infarction by 15% and the risk of hospitalization for stroke by 28% (48).

Many previous findings were restricted to patients with diabetes or

with previous CVD (49-51). Ho et al. (50) showed that medication nonadherence was correlated with higher risk for all-cause hospitalization (HR: 1.37, 95% CI: 1.25 - 1.51) and for all-cause mortality (HR: 1.77, 95% CI: 1.45 - 2.15) in patients with diabetes mellitus. Rasmussen et al. (49) reported that compared with those with high levels of adherence, the risk of mortality was 13% higher among patients with poor adherence in survivors of AMI (HR: 1.13, 95% CI: 1.03 - 1.25). Gislason et al. (51) showed that nonadherence with the renin-angiotensin system inhibitors, beta blocker was associated with increased mortality in heart failure patients (renin-angiotensin system inhibitor: HR: 1.37, 95% CI: 1.31 - 1.42, beta-blockers: HR: 1.25, 95% CI: 1.19 - 1.32).

However, 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 (27, 45, 46) or all-cause mortality (31, 43). Degli Esposti et al.(43) showed that the risk of the combined outcome of all-cause death, stroke, or AMI decreased with an increase in medication adherence from good adherence (HR: 0.69, 95% CI: 0.58 - 0.81) to 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) (29). 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 up to 7years); in addition, the study population was large and accurately represented South Korean hypertensive patients by drawing on the claim data of the KNHI.

To verify the robustness of our findings, we calculated HRs to evaluate association between adherence to antihypertensive medication and non-CVD mortality or non-CVD hospitalization. According to expectation, the cancer mortality and hospitalization risks were not associated with antihypertensive medication adherence. The result provides further support for our finding regarding the association of adherence to CVD mortality. However, the risk of non-CVD mortality and non-disease mortality (accidents) were also increased, similarly to the outcome of all-cause mortality. It is possible that adherent patients are more likely to adopt a healthier behavioral life style (i.e. healthy adherer effect), to contribute to decrease all-cause mortality. Future study is needed to investigate the role of medication adherence including lifestyle adjustments in CVD outcome.

Our study used three levels of adherence, whereas previous studies referred to two levels using a cutoff value of 0.8 (27, 28, 30, 46, 47). The division into three 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 (52).

To identify factors affecting medication adherence, we conducted

multiple logistic regression analysis. The risk factors affecting nonadherence to antihypertensive medication in the present study were women, younger age, low income level, high Charlson's comorbidity score, rural residential area and taking one class of antihypertensive medication. Our study provides further support for previous findings regarding the predictors of adherence to antihypertensive medication. The World Health Organization has categorized potential reasons for medication nonadherence into 5 broad groupings that include patient, condition, therapy, socioeconomic, and health system-related factors (53). Patient factors associated with medication nonadherence include younger age, nonwhite race, sex. Previous studies have found that increased age was associated with adherence to antihypertensive medication (18, 27). The difference of adherence to antihypertensive medication between sex was observed in previous studies (29, 31). Chronic diseases with long-term medication have also been associated with nonadherence. Previous researches showed that comorbidities are associated with adherence to antihypertensive medication (27, 29). However, unlike previous studies, our study showed that rate of medication nonadherence was correlated with increasing Charlson's comorbidity score. (Charlson's comorbidity score =1: OR: 1.25, 95% CI: 1.18-1.32, Charlson's comorbidity score = 2: OR: 1.43, 95% CI: 1.31 - 1.55, Charlson's comorbidity score ≥3: OR: 1.68, 95% CI: 1.50 - 1.88). For therapy-related factors, the class of antihypertensive medication, the complexity of the regimen and the perceived side effects can impact

adherence (19, 29, 54). Our study provides further support for previous findings. Patients taking more than two different classes of antihypertensive medications had a lower risk of nonadherence than patients taking one class of antihypertensive medication. The risk of nonadherence was relatively low in patients who take an angiotensin receptor blocker. Socioeconomic factors such as lower income level have been correlated with nonadherence.

## 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 (9). 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 is more frequently used and is an efficient indirect method for assessing medication adherence in a large population. CMA is a well-validated measurement tool and is useful for measuring adherence over a long period (23). 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 (25, 54).

Second, a formal diagnosis of hypertension was not available. In the

present study, the prescription of an 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 SouthKorea.However,Bullanoetal.(55) 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 kappa score was 0.65 (55). Other studies identified hypertensive patients as those who had at least two claims for outpatient services or one claim for hospitalization and had at least one prescription (14, 34), which was similar as our definition of hypertensive patients. The condition of at least two claims for outpatient services was included to reduce the incidence of false-positive diagnoses or misclassification.

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 (6). Another RCT suggested substantial benefit of various antihypertensive drugs even when reductions of blood pressure are small (56). 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 (29). 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 (57). Thus, lack of blood pressure data is 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.

# Conclusion

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 7years 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 regarding the need to improve compliance with therapy.

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# 국문 초록
# 고혈압환자에서 고혈압 약물 순응도가 심혈관질환 사망 및 입원에 미치는 영향

**목적**: 항고혈압제에 대한 약물 순응도는 심혈관계 질환과 관련이 있음이 알려져 있다. 본 연구는 한국인 고혈압 환자에서 고혈압 약물 순응도가 전체 심혈관계 질환으로 인한 사망뿐만 아니라 각 심혈관계 질환 별 (허혈성 심질환, 뇌출혈, 뇌경색) 사망 및 입원에 미치는 영향을 알아보고자 한다.

방법: 국민건강보험공단에서는 무작위 추출을 통해 2002년도 건강보험 자격 대상자 중 3%를 표본 추출하여 표본 코호트를 구축하였다. 건강보험 공단으로부터 2002년부터 2010년까지 추적 관찰한 표본 코호트 자료를 받아, 이중 20세 이상 성인으로서 2003년에서 2004년도에 고혈압으로 처음 진단 받고 항고혈압제를 처방 받은 환자들을 대상으로 분석을 하였다. 약물 순응도는 항고혈압제 처방에 대한 청구자료를 이용하여, 누적 약물 순응도 (cumulative medication adherence: CMA)방법으로 계산하였다. 약물 순응도의 기준은 누적약물 순응도 80%와 50%를 기준으로 나누었다. 고혈압 약물 순응도와 심혈관계 질환 사망 및 입원 위험을 분석하기 위하여 콕스 비례위험 모형을 이용한 생존 분석을 시행하였다. 또한, 약물 순응도에 영향을 미치는 요인을 파악하기 위하여 다중 로지

스틱 회귀 분석을 시행하였다.

결과: 약물 순응도가 낮은 환자 군에서 허혈성 심장 질환 (HR: 1.49, 95% CI: 1.09 - 2.04, P for trend=0.023), 뇌출혈(R: 2.71, 95% CI: 1.65 - 4.47, P for trend<0.001), 심부전 (HR: 2.07, 95% CI: 1.05-6.74, P for trend=0.030) 으로 인한 사망 위험이 약물순응도가 높은 환자 군에서 보다 증가하였다. 심혈관 질환으로 인한 입원 위험도 약물 순응도가 낮은 군에서 유의하게 증가하였다. 항고혈압 약제를 처방 받은 첫 2년 간의 약물 순응도에 영향을 미치는 요인으로는 성별, 연령, 소득 수준, 거주 지역, 복용 약물 개수 등이 있었다. 높은 소득 수준(OR: 0.82, 95% CI: 0.77 - 0.86), 2개 이상의 항고혈압제 복용(OR: 0.86, 95% CI: 0.82 - 0.91), 고지혈증 동반 (OR: 0.90, 95% CI: 0.83 - 0.96) 등은 높은 약물 순응도와 관련이 있었다.

결론: 낮은 고혈압 약물 순응도는 각 심혈관계 질환의 사망 위험과 입원 위험을 증가시킨다. 고혈압 약물의 순응도를 지속적으로 평가하고, 약물 순응도를 높이기 위하여 노력하는 것은 고혈압 치료 및 심혈관계 질환을 예방하기 위해 중요하다.

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**주요어:** 심혈관계 질환, 입원, 약물 순응도, 항고혈압제, 뇌졸중

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