Effect of Adherence to Antihypertensive Medication on the Long-Term Outcome After Hemorrhagic Stroke in Korea

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Abstract—Hypertension is the single most important risk factor for hemorrhagic stroke, a leading cause of mortality and disability worldwide. Adherence to antihypertensive medication is essential to achieving strict blood pressure control, but poor adherence is common in clinical practice. We evaluated adherence to antihypertensive medication in patients with acute hemorrhagic stroke and its effects on long-term outcome. This was a retrospective cohort study based on a nationwide health insurance claims database in South Korea. We included 1872 hypertensive patients who were admitted with acute hemorrhagic stroke during 2002 to 2013 (1354 cases of intracerebral hemorrhage and 518 cases of subarachnoid hemorrhage). Adherence to antihypertensive medication was calculated using the proportion of days covered by any antihypertensive medication throughout the follow-up period (categorized into poor <40%; intermediate 40%–80%; good >80%) and treated as a time-dependent variable. Primary outcome was defined as a composite of recurrent stroke (hemorrhagic or ischemic), myocardial infarction, or all-cause mortality. Time-dependent Cox proportional hazard regression analyses were performed. During the mean follow-up period of 4.45 years, 634 patients had the primary outcome. The proportion of patients with good adherence to antihypertensive medication was 46.8% at 1 year, 43.2% at 3 years, and 41.7% at 5 years of follow-up. Compared with good adherence, the adjusted hazard ratio (95% confidence interval) for the primary outcome was 1.80 (1.49–2.16) for poor adherence and 1.56 (1.27–1.93) for intermediate adherence. **(*Hypertension*. 2018;72:391-398. DOI: 10.1161/HYPERTENSIONAHA.118.11139.)**

● **Online Data Supplement**

Key Words: hypertension ■ medication adherence ■ mortality ■ prognosis ■ stroke

Because of the high risk of fatality and long-term disability, hemorrhagic stroke is a major global health problem.[1] Recurrent stroke is frequent after hemorrhagic stroke and generally has greater severity and higher mortality.[2] Hypertension is the strongest contributor to the development and recurrence of hemorrhagic stroke.[3,4] The identification and strict control of hypertension is crucial for the prevention of hemorrhagic stroke. However, uncontrolled hypertension is common in clinical practice and leads to increased risks of cardiovascular and cerebrovascular diseases including hemorrhagic stroke.[5] Emerging data report that nonadherence to antihypertensive medication is the leading cause of uncontrolled hypertension and resultant cardiovascular risk.[6,7] Despite the clinical importance and high prevalence of hypertension in patients with hemorrhagic stroke, there are insufficient data for the adherence to antihypertensive medication after hemorrhagic stroke. Here, we investigated the adherence to antihypertensive medication after acute hemorrhagic stroke in the real world using the nationwide health claims database in Korea. We aimed to evaluate the effect of antihypertensive medication adherence on the long-term outcome of these patients.

Methods

Data Source

Data can be accessed through the homepage of National Health Insurance Sharing Service (http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do). To gain access to the data, a completed application form, a research proposal, and the applicant's approval document from the institutional review board should be submitted to and reviewed by the inquiry committee of research support in National Health Insurance Service (NHIS). Currently, use of NHIS data is allowed only for Korean researchers. This retrospective cohort study used the National Health Insurance Service–National Sample Cohort (NHIS-NSC), a population-based sample cohort database of 1 025 340 participants.[8] The subjects comprised ≈2.2% of the total eligible Korean population in 2002, and the data were sampled randomly and stratified by sex, age, and household income. The NHIS-NSC consisted of health claims data between 2002 and 2013, including hospital visits, medical procedures, prescriptions, diagnoses, and demographic information, as well as sex, age, household income, and death statistics. Diagnoses made at the hospital visit were recorded according to the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*). The NHIS-NSC data were fully anonymized and did not contain any identifiable information. This study was approved and informed consent was waived by the Institutional Review Board of Bundang CHA Medical Center.

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Study Population

We included patients who were ≥20 years of age with acute hemorrhagic stroke defined as hospitalization (admission or visit to the emergency department) with a primary diagnosis of nontraumatic hemorrhagic stroke (*ICD-10* code I60: nontraumatic subarachnoid hemorrhage [SAH]; I61: nontraumatic intracerebral hemorrhage [ICH]) between 2002 and 2013.[9] We included only patients who underwent brain computed tomography or magnetic resonance imaging during hospitalization because of the assumption that patients with acute hemorrhagic stroke should undergo brain imaging.[10] Patients with a diagnosis of hemorrhagic stroke during January to June 2002 were excluded to create a 6-month washout period. These approaches were intended to exclude chronic patients who were hospitalized for rehabilitation or other medical problems with a prior diagnosis of hemorrhagic stroke. Because antihypertensive medication was recommended for patients with hypertension, we included only those with a diagnosis of hypertension (*ICD-10* codes I10–I15) who had received oral antihypertensive medication (calcium channel blockers [CCB], angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB], diuretics, β-blockers, α-blockers, and vasodilators) at or before the index stroke. Patients who were followed up for <3 months because of clinical outcome or censoring were excluded because the short period might be inappropriate for representing long-term medication adherence.

Study Outcomes

The primary outcome was a composite of recurrent stroke (hemorrhagic or ischemic), myocardial infarction (MI), or all-cause death after the index date, whichever occurred first. Patients were followed up until the development of the clinical outcomes, loss of participant eligibility, or December 2013. Recurrent stroke was defined as hospitalization with a primary diagnosis of I60–I63 and having undergone brain computed tomography or magnetic resonance imaging during the hospitalization. MI was defined as hospitalization with a primary diagnosis of I21. The diagnostic accuracy for stroke and MI in the NHIS was validated in prior studies.[11,12] Date and cause of death for each patient were obtained from death statistics in the NHIS-NSC. As one of secondary outcome, we defined cardiovascular mortality as in the cases whose cause of death was recorded as *ICD-10* codes I00–I99 in the death statistics. Causes of death in the death statistics in Korea have been previously reported to be reliable.[13]

Adherence to Antihypertensive Medication as Time-Dependent Variable

In Korea, antihypertensive medication should be prescribed by physicians in hospitals. Patients visiting pharmacies can receive medications by submitting the paper prescriptions issued by the physicians. Refill program in pharmacy based on prior prescription is not allowed in Korea. Because NHIS is a single-payer program in Korea, NHIS-NSC contains the whole prescription records for the patient (drug name, dose, date, and duration). In this study, adherence to antihypertensive medication was calculated using the prescription records issued by physicians. On each day of follow-up, the use of antihypertensive medication was determined whether the day was covered with the prescribed antihypertensive medication of any class. If there was overlap of the same class of antihypertensive medication in prescription, the overlapped period was delayed under the assumption that there was an early refill. As marker of adherence, the proportion of days covered (PDC) by antihypertensive medication from the index date to a given day were calculated on every day of follow-up (PDC_{fu}) and was treated as a time-dependent variable.[14] The calculation of PDC_{fu} is explained in more detail in the Table S1 in the online-only Data Supplement. PDC_{fu}, a marker of adherence to antihypertensive medication, was classified into poor adherence (PDC <40%), intermediate adherence (PDC 40%–80%), and good adherence (PDC >80%). PDC >80% was established as a reliable cutoff for good adherence.[10,15]

Other Time-Fixed Variables

Type of hemorrhagic stroke was divided into SAH and ICH according to the primary diagnostic code of the index hemorrhagic stroke.[9] As baseline characteristics, data for sex, age, household income, and length of hospital stay at index hemorrhagic stroke were collected. Definition for the time-fixed variables and explanation for statistical method are available in the online-only Data Supplement.

Results

Baseline Characteristics

The final data set included 1872 hypertensive patients with acute hemorrhagic stroke (1354 cases of ICH and 518 cases of SAH; Figure 1). Median age at hemorrhagic stroke was 60 to 64 years (interquartile range: 50–54 years; 70–74 years), and 47.8% were male (Table 1). Compared with patients with SAH, those with ICH were older, more male, and had diabetes mellitus and shorter length of hospital stay at index stroke. According to the PDC by antihypertensive medication over the first 3-month after the hemorrhagic stroke (PDC_{3month}), the proportion of patients with poor (<40%), intermediate (40%–80%), and good (>80%) adherence was 28.5%, 22.0%, and 49.5%, respectively. When we evaluated the proportion of patients who had good adherence to individual class of antihypertensive medication over the first 3 months (PDC_{3month} by individual class), those with good adherence to CCB was most the frequent, and the next was ACE inhibitors/ARB (Table 1).

Regarding the comparison of characteristics by adherence category over the first 3 months (Table 1; Table S2), patients with SAH had lower adherence to antihypertensive mediation compared with those with ICH. The proportion of patients with good adherence to individual class of antihypertensive medication was lower in SAH compared with ICH, regardless of the class. The presence of diabetes mellitus and longer stay in hospital were associated with a higher adherence to antihypertensive medication over the first 3 months. Other characteristics were not significantly associated with medication adherence.

Time Trend of Adherence to Antihypertensive Medication

Table 2 demonstrates the trend of adherence to the antihypertensive medication during the follow-up period. Over

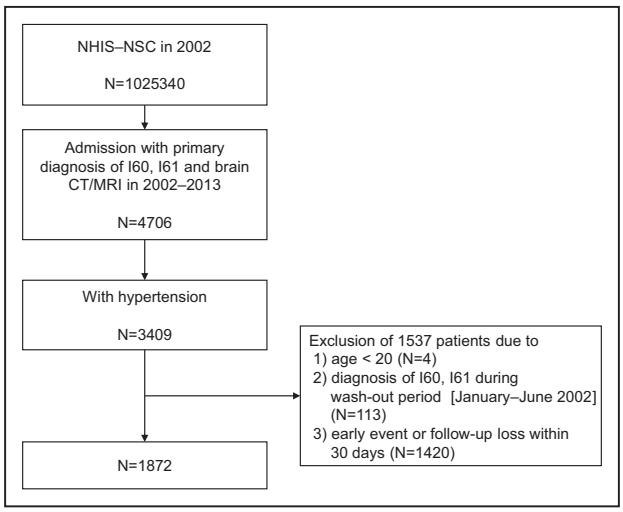

Figure 1. Flow chart of inclusion and exclusion criteria. CT indicates computed tomography; MRI, magnetic resonance imaging; and NHIS-NSC, National Health Insurance Service–National Sample Cohort.

Table 1. Clinical Characteristics of the Included Patients

Variable	All (N=1872)	ICH (n=1354)	SAH (n=518)	*P* Value*
Sex, male	894 (47.8)	702 (51.8)	192 (37.1)	<0.001
Age	60–64 (50–54; 70–74)	60–64 (50–54; 70–74)	55–59 (45–49; 65–69)	<0.001
Diabetes mellitus	370 (19.8)	291 (21.5)	79 (15.3)	0.003
Myocardial infarction	125 (6.7)	96 (7.1)	29 (5.6)	0.292
Household income				0.165
Low	522 (27.9)	394 (29.1)	128 (24.7)	
Middle	633 (33.8)	449 (33.2)	184 (35.5)	
High	717 (38.3)	511 (37.7)	206 (39.8)	
Year of admission				0.039
2002–2005	685 (36.6)	518 (38.3)	167 (32.2)	
2006–2009	601 (32.1)	417 (30.8)	184 (35.5)	
2010–2013	586 (31.3)	419 (30.9)	167 (32.2)	
Length of hospital stay, d				<0.001
<16	686 (36.6)	536 (39.6)	150 (29.0)	
16–27	594 (31.7)	385 (28.4)	209 (40.3)	
>27	592 (31.6)	433 (32.0)	159 (30.7)	
Adherence to antihypertensive medication over the first 3 mo				<0.001
Poor (PDC_{3mo} <40%)	534 (28.5)	333 (24.6)	201 (38.8)	
Intermediate (PDC_{3mo} 40%–80%)	412 (22.0)	279 (20.6)	133 (25.7)	
Good (PDC_{3mo} >80%)	926 (49.5)	742 (54.8)	184 (35.5)	
Good adherence (PDC_{3mo} >80%) to individual class of antihypertensive medication over the first 3 mo				
Calcium channel blocker	593 (31.7)	460 (34.0)	133 (25.7)	<0.001
ACE inhibitors/ARB	470 (25.1)	414 (30.6)	56 (10.8)	<0.001
Diuretics	182 (9.7)	156 (11.5)	26 (5.0)	<0.001
β-Blocker	174 (9.3)	160 (11.8)	14 (2.7)	<0.001
α-Blocker	18 (1.0)	16 (1.2)	2 (0.3)	0.189
Vasodilator	25 (1.3)	20 (1.5)	5 (1.0)	0.523

Data are represented as number (%) or median (interquartile range). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ICH, intracerebral hemorrhage; PDC_{3mo}, proportion of days covered by antihypertensive medication over the first 3 mo after index hemorrhagic stroke; and SAH, subarachnoid hemorrhage.

**P* value between SAH and ICH groups.

the follow-up period, the proportion of patients with good adherence to the antihypertensive medication (PDC_{fu} >80%) remained at <50%. The proportion of patients with good adherence was only 46.8% at 1 year, 43.2% at 3 years, and 41.7% at 5 years of follow-up.

Primary Outcome by Adherence to Antihypertensive Medication

During the follow-up period of 4.45±3.33 years (mean±SD), 634 patients had the primary outcome (233 cases of recurrent stroke, 10 cases of MI, and 391 cases of all-cause death; considering only the first event per patient). Figure 2 illustrates the event-free survival plot of adherence to antihypertensive medication treated as a time-dependent variable. There was a significant difference in event-free survival according to the adherence to antihypertensive medication (*P*<0.001). In the multivariate Cox regression models (Table 3), there was an inverse relationship between the adherence to antihypertensive medication and the risk of primary outcome after hemorrhagic stroke. Compared with the good adherence, the adjusted hazard ration (HR) (95% confidence interval [CI]) for the poor and intermediate adherence were 1.80 (1.49–2.16) and 1.56 (1.27–1.93), respectively. When we set the reference to poor adherence in the model, the adjusted HR (95% CI) for the intermediate adherence was 0.87 (0.71–1.07). In the subgroup analysis of SAH and ICH (Table 3), the significant risk with poor adherence compared with good adherence was consistent. However, the increased risk with intermediate adherence compared with good adherence was only significant in patients with ICH (adjusted HR [95% CI], 1.66 [1.32–2.07]) but not in those with SAH (adjusted HR [95% CI], 1.03 [0.57–1.88]).

Table 2. Adherence to Antihypertensive Medication During the Follow-Up Period

Type of Hemorrhagic Stroke	Adherence to Antihypertensive Medication	Time From Hemorrhagic Stroke						
		3 mo	6 mo	1 y	2 y	3 y	4 y	5 y
ICH+SAH (N=1872)	PDC_{fu} <40%	534 (28.5)	539 (31.2)	527 (34.8)	457 (36.0)	382 (35.2)	317 (35.8)	261 (35.6)
	PDC_{fu} 40%–80%	412 (22.0)	349 (20.2)	278 (18.4)	244 (19.2)	235 (21.6)	195 (22.0)	167 (22.8)
	PDC_{fu} >80%	926 (49.5)	841 (48.6)	709 (46.8)	567 (44.7)	469 (43.2)	373 (42.1)	306 (41.7)
	Number at risk	1872	1729	1514	1268	1086	885	734
ICH (n=1354)	PDC_{fu} <40%	333 (24.6)	331 (26.6)	332 (30.8)	290 (32.9)	246 (32.9)	199 (33.1)	167 (33.3)
	PDC_{fu} 40%–80%	279 (20.6)	260 (20.9)	215 (20.0)	181 (20.5)	167 (22.4)	143 (23.8)	122 (24.3)
	PDC_{fu} >80%	742 (54.8)	653 (52.5)	530 (49.2)	411 (46.6)	334 (44.7)	260 (43.2)	213 (42.4)
	Number at risk	1354	1244	1077	882	747	602	502
SAH (n=518)	PDC_{fu} <40%	201 (38.8)	208 (42.9)	195 (44.6)	167 (43.3)	136 (40.1)	118 (41.7)	94 (40.5)
	PDC_{fu} 40%–80%	133 (25.7)	89 (18.4)	63 (14.4)	63 (16.3)	68 (20.1)	52 (18.4)	45 (19.4)
	PDC_{fu} >80%	184 (35.5)	188 (38.8)	179 (41.0)	156 (40.4)	135 (39.8)	113 (39.9)	93 (40.1)
	Number at risk	518	485	437	386	339	283	232

Data are represented as number and proportion (%) of patients with the adherence among those who remained at risk without censoring or event outcome at the given time point. PDC_{fu} is defined as proportion of days covered by antihypertensive medication over the period of follow-up between index date of hemorrhagic stroke and the given time point (3 mo, 6 mo, 1 y, 2 y, 3 y, 4 y, and 5 y). ICH indicates intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

Comparison of Good Adherence to CCB and ACE Inhibitors/ARB

CCB and ACE inhibitors/ARB were the 2 most commonly prescribed antihypertensive medication in this study (Table 1). To evaluate the potential difference on the risk of primary outcome by the 2 class with good adherence, we further subdivided the good adherence to antihypertensive medication (PDC_{fu} by any antihypertensive medication >0.8) according to the class-specific PDC_{fu} by CCB and ACE inhibitors/ARB. In the multivariate time-dependent Cox regression models using the subclassification (Table S3), (PDC_{fu} by ACE inhibitors/ARB >0.8 and PDC_{fu} by CCB ≤0.8) were at lower risk of primary outcome (adjusted HR [95% CI], 0.69 [0.49–0.98]) compared with (PDC_{fu} by CCB >0.8 and PDC_{fu} by ACE inhibitors/ARB ≤0.8).

Secondary Outcome Analysis

During the follow-up period, there were 233 patients with recurrent stroke, 12 patients with MI, and 471 patients with all-cause death, including 302 cardiovascular deaths. In the secondary outcome analyses using individual Cox regression models (Table S4), there was significantly increased risk of cardiovascular mortality (adjusted HR [95% CI] compared with good adherence, 2.44 [1.86–3.20]) and all-cause mortality (adjusted HR [95% CI] compared with good adherence, 2.25 [1.80–2.80]) with poor adherence to antihypertensive medication. The risk for recurrent stroke showed increasing tendency with poor adherence (adjusted HR [95% CI], 1.30 [0.96–1.75]), but it did not reach statistical significance. The risk for MI was not significantly associated with adherence to antihypertensive medication.

Discussion

This cohort study using a nationwide health claims database found that adherence to antihypertensive medication was frequently suboptimal even after acute hemorrhagic stroke. Poor adherence to antihypertensive medication was significantly associated with increased risk for the primary outcome after hemorrhagic stroke. In the subgroup analyses, intermediate adherence to antihypertensive medication was at an increased risk compared with good adherence in ICH but not in SAH. We supposed that the effect of adherence to antihypertensive medication may vary according to the type of hemorrhagic stroke and underlying cause. There

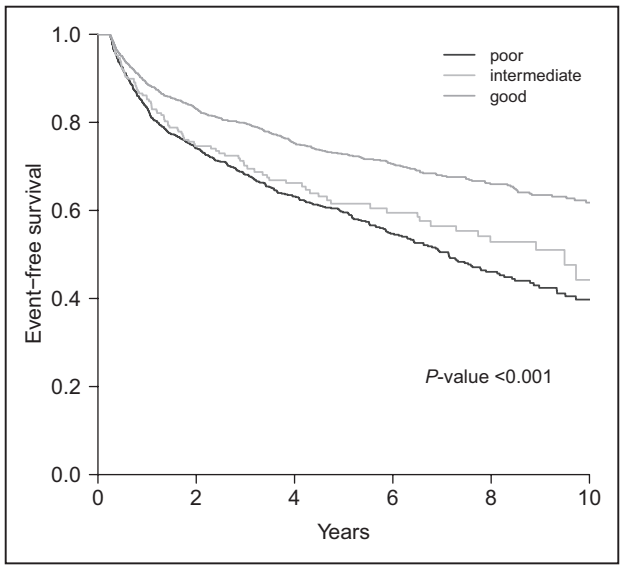

Figure 2. Plot of event-free survival after hemorrhagic stroke according to the antihypertensive medication adherence with the Simon and Makuch method. Based on proportion of days covered (PDC) during follow-up period, adherence to antihypertensive medication are classified into poor (PDC <40%), intermediate (PDC 40%–80%), and good (PDC >80%). *P* value between the survival curves is derived by the Mantel–Byer test.

Table 3. Effects of Adherence to Antihypertensive Medication After Hemorrhagic Stroke

Adherence to Antihypertensive Medication	Crude HR (95% CI)			Adjusted HR (95% CI)*		
	All (N=1872)	ICH (n=1354)	SAH (n=518)	All (N=1872)	ICH (n=1354)	SAH (n=518)
Poor (PDC_{fu} <40%)	1.70 (1.41–2.04)	1.86 (1.52–2.28)	1.59 (1.04–2.44)	1.80 (1.49–2.16)	1.80 (1.46–2.21)	1.74 (1.14–2.66)
Intermediate (PDC_{fu} 40%–80%)	1.58 (1.28–1.95)	1.67 (1.33–2.09)	1.08 (0.60–1.93)	1.56 (1.27–1.93)	1.66 (1.32–2.07)	1.03 (0.57–1.88)
Good (PDC_{fu} >80%)	Ref	Ref	Ref	Ref	Ref	Ref

Data are derived by Cox proportional hazard regression model treating adherence to antihypertensive medication as time-dependent variable. Primary outcome is a composite of recurrent stroke, myocardial infarction, and all-cause death. CI indicates confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; PDC_{fu}, proportion of days covered by antihypertensive medication over the period of follow-up; and SAH, subarachnoid hemorrhage.

*Adjusted for type of hemorrhagic stroke (SAH, ICH), sex, age, diabetes mellitus, prior myocardial infarction, household income, length of hospital stay, and year of index hemorrhagic stroke.

was heterogeneity of underlying characteristics and coexisting risk factors between patients with ICH and SAH. Chronic hypertension can induce arteriosclerotic degenerative changes and accumulation of amyloid deposits (cerebral amyloid angiopathy) in cerebral arterioles, which are 2 common underlying pathologies in ICH.[2] Lowering blood pressure is likely to reduce the risks of both types of ICH.[16] Although hypertension is a risk factor for formation and rupture of cerebral aneurysm, which is the most common cause of nontraumatic SAH, the recurrence risk after SAH might be more influenced by the presence and extent of the underlying structural lesion than control of hypertension during follow-up. Unfortunately, because of the limited data from the health insurance claims database, we could not further evaluate whether underlying cause and structural lesion of hemorrhagic stroke (lobar ICH, nonlobar ICH, aneurysmal SAH, nonaneurysmal SAH, etc) influence the effect of adherence to antihypertensive medication on long-term outcome.

In the secondary outcome analysis, poor adherence to antihypertensive medication was significantly associated with all-cause and cardiovascular mortality. However, in recurrent stroke and MI, we could not find significant association with the adherence. Small number of the outcomes and sudden fatal outcome without hospitalization, not properly captured as recurrent events with health insurance claims database, may lead to negative results for the outcomes. One more interesting finding was that good adherence to ACE inhibitors/ARB was at lower risk of primary outcome than good adherence to CCB, which suggests for potential class effect of ACE inhibitors/ARB to the patients with hemorrhagic stroke. It is unclear which class of antihypertensive medication is the most preventive after stroke. Generally, adequate control of blood pressure is considered to be more important than class-specific effect in antihypertensive medication.[17] There are some experimental data supporting that renin-angiotensin system inhibition by ACE inhibitors/ARB can reduce vascular oxidative stress, inflammation, and nephropathy and modify endothelial dysfunction and vascular remodeling, which may lead to class-specific vascular protective effects beyond control of blood pressure.[18] Perindopril Protection Against Recurrent Stroke Study was a randomized trial that evaluated the treatment effect of perindopril (ACE inhibitor) plus indapamide (diuretics) in patients with prior cerebrovascular disease. Use of perindopril plus indapamide reduced the risk of ICH by 50% (cerebral amyloid angiopathy–related ICH by 77% and hypertension-related ICH by 46%) compared with placebo.[16] Because of the retrospective observational nature and lack of data for blood pressure during follow-up period, we could not conclude the class-specific vascular protective effects of ACE inhibitors/ARB after hemorrhagic stroke. There is need for further studies to answer the unsolved issues from this study.

From the results of many clinical trials and epidemiological evidence, hypertension has been established as the most important risk factor for stroke.[1,3,4] Randomized controlled trials have proven that the use of antihypertensive medication can reduce major cardiovascular events including stroke and mortality in hypertensive patients.[19] However, uncontrolled blood pressure is frequently encountered in clinical practice.[4] Analysis of the National Health and Nutrition Examination Survey data of the United States from 2013 to 2014 revealed that only 54% of adults with hypertension were under control (systolic blood pressure <140 mm Hg; diastolic blood pressure <90 mm Hg), which means that about a half of cases remain uncontrolled.[20] Uncontrolled hypertension, a major risk factor for recurrent stroke and mortality, is also frequent in stroke survivors.[21] A systematic review using data from randomized controlled clinical trials of secondary stroke prevention clearly demonstrated that the extent of blood pressure reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular and cardiovascular events.[22] The strength of the positive association between hypertension and risk for hemorrhagic stroke is even greater than that observed for ischemic stroke.[23,24]

Poor adherence to antihypertensive medication, which is common in clinical practice, is the leading cause of uncontrolled blood pressure and resultant cardiovascular risk but often left unrecognized.[25,26] Nonadherence to medication is a multifactorial problem, which includes relationship between the physician and patient, lack of education for medication, problem in access to healthcare service, coexisting medical condition, medication-related side effects, complex medical regimen, drug cost, and socioeconomic factors.[27] In this study, the proportion of patients with good adherence to antihypertensive medication was <50% during the long-term follow-up period after hemorrhagic stroke. Despite the clear benefits of antihypertensive medication for reducing blood pressure and cardiovascular risk, poor adherence to an antihypertensive medication regimen is a consistent finding across various studies.[6,28,29] In a recent population-based cohort study of Medicare fee-for-service beneficiaries who were newly diagnosed with hypertension and initiated antihypertensive medication in

2008 to 2009, ≈60% had high adherence (PDC ≥80%) during follow-up.[30] A retrospective cohort study using the PHARMO record linkage system also showed that only 39% of patients who started antihypertensive drugs continued the medication during the 10-year follow-up (≈22% discontinued temporarily and 39% of patients discontinued permanently).[31] Poor adherence is common even after acute vascular events including MI and stroke.[28,32] The Registry of the Canadian Stroke Network reported that the proportion of high adherence (PDC >80% for 1 year) was 61.8% to 75.8% in acute stroke patients who received antihypertensive medication.[33] The analysis of medication adherence after acute ischemic stroke based on NHIS-NSC data in Korea revealed that the proportion of hypertensive patients with good adherence to antihypertensive medication for 1 year was 50.6%.[10]

The adverse impact of poor adherence to antihypertensive medication has been well established in various patient populations including those with newly treated hypertension, coronary artery disease, and ischemic stroke.[10,15,28,29] Early discontinuation of antihypertensive medication was a strong risk factor for subsequent MI and stroke.[34] Poor adherence to antihypertensive medication can increase risk of heart failure and end-stage renal disease.[35–37] Hypertension is a major cause of hemorrhagic stroke, and proper control of hypertension is the cornerstone of secondary prevention.[23,38] However, there is only limited data for the effects of hypertension control and adherence to antihypertensive medication after hemorrhagic stroke. In a retrospective study of 51 patients with hemorrhagic stroke, those with lower diastolic blood pressure during follow-up period had less frequent recurrence.[39] A prior cohort study including 162 patients with spontaneous ICH demonstrated that blood pressure control was extremely poor after ICH; fewer than 20% of ICH survivor patients had normal blood pressure (<120/80 mm Hg) at 30 days or 1 year.[40] Another recent observational study of 1145 survivors of ICH also found that fewer than 50% of ICH patients achieved consistent blood pressure control.[2] In the study, inadequate blood pressure control during follow-up was strongly associated with an increased risk of both lobar and nonlobar ICH recurrence.[2] These data suggested that inadequate control of blood pressure was common after ICH, and strict control of blood pressure may reduce the risk of recurrence. After acute aneurysmal SAH, hypertension is associated with increased risk of early rebleeding.[41] However, there is a lack of evidence for whether the long-term proper control of hypertension can prevent recurrent SAH.[42] One follow-up screening study after SAH using computed tomographic angiography demonstrated that hypertension was a significant risk factor for formation or enlargement of aneurysm (adjusted HR [95% CI], 2.3 [1.1–4.9]), which suggested that hypertension should be closely monitored and treated for the prevention of recurrent SAH.[43]

In this study, we followed up >1800 hypertensive patients with ICH or SAH over a mean follow-up period of 4.45 years using the nationwide health insurance claims data. We could access the long-term medication adherence to antihypertensive medication based on prescription records in the longitudinal cohort. We added evidence that poor adherence to antihypertensive medication after hemorrhagic stroke was common in clinical practice, and it was strongly associated with increased risk of adverse events. The finding of poor adherence to antihypertensive medication could be one explanation for the high prevalence of inadequate blood pressure control after hemorrhagic stroke in the prior studies. Considering the deteriorating effects of uncontrolled hypertension in hemorrhagic stroke and the increased risk on nonadherence, there is an urgent need to identify nonadherence and initiate interventions to encourage adherence to antihypertensive medication, which may improve long-term prognosis. Although the effects of interventions on adherence are not well documented, regular program access and patient feedback about medication adherence, education, the avoidance of polypharmacy, reducing dosing frequency, and community pharmacist assistance may be helpful for improving medication adherence to antihypertensive and evidence-based cardiovascular medications and eventually cardiovascular prognosis.[44,45]

We should acknowledge some potential limitations of this study. Because this study had retrospective cohort design, we only demonstrated that poor adherence to antihypertensive medication was associated with an increased risk of cardiovascular events or all-cause mortality after hemorrhagic stroke, but we could not conclude a causal relationship between them. This study lacked some important risk factors that were unavailable in the health insurance claims data, such as underlying cause of hemorrhagic stroke, severity of hemorrhagic stroke, radiological findings, cigarette smoking, and blood pressure values during follow-up. According to the unavailable data of underlying cause and the presence of potential structural pathology (amyloid angiopathy, arteriovenous malformation, and aneurysms), effect of adherence to antihypertensive medication may vary after hemorrhagic stroke. Outcome measure was performed based on primary diagnostic code on hospital visit. Although there were prior validation studies for detection of cardiovascular outcomes based on the diagnostic code in the NHIS, nonfatal outcomes not associated with the hospital visit may not have been captured.[11,12] To measure medication adherence, we used prescription records in the NHIS-NSC. There might be gaps between the prescription records issued by physicians and the patients' actual medication usage. Poor adherence to antihypertensive medication might reflect underlying medical conditions such as a functional disability, which is common after stroke and can confound adherence.[7] Finally, our study was based on Asian population in Korea. There are differences in epidemiological features with hemorrhagic stroke and healthcare system for medications by countries and populations.[24] Therefore, there is a need for caution in interpreting our findings and applying it to other populations.

Perspectives

This retrospective cohort study demonstrated that poor adherence to antihypertensive medication is common even after acute hemorrhagic stroke and strongly associated with adverse events. As with our findings, substantial evidence has shown that poor adherence to antihypertensive medication is a critical contributor to uncontrolled hypertension and further cardiovascular risk. To obtain strict control of blood pressure and cardiovascular risk, health professionals should be concerned about patient's adherence to antihypertensive medication and strive to help improve them.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Even after acute hemorrhage stroke, poor adherence to antihypertensive medication regimens is commonly encountered in clinical setting. Throughout the follow-up period of >5 years, the proportion of patients with good adherence was <50%.

What Is Relevant?

- A poor adherence to antihypertensive medication is strongly associated with a worse outcome in hypertensive patients with acute hemorrhagic stroke.

Summary

Poor adherence to an antihypertensive medication regimen is a strong risk factor for worse outcome after hemorrhagic stroke and might be a potential treatment target for improving long-term prognosis.

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Effect of Adherence to Antihypertensive Medication on the Long-Term Outcome After Hemorrhagic Stroke in Korea

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Title: EFFECT OF ADHERENCE TO ANTIHYPERTENSIVE MEDICATION ON THE LONG-TERM OUTCOME AFTER HEMORRAGIC STROKE IN KOREA

Short title: Antihypertensive adherence after ICH and SAH

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Supplemental method

Definition for covariates

Age was grouped into 5-year periods in the National Health Insurance Service–National Sample Cohort (NHIS-NSC), which are treated as continuous variable in the statistical analysis. In NHIS-NSC, the household income level is recorded as a continuous variable (from 0 for medical aid to 10 for the highest income level). We stratified the household income level into tertile groups (0–3: low, 4–7: middle, and 8–10: high) for analysis. Patients were grouped into tertiles by the length of hospital stay at index hemorrhagic stroke (<16 days, 16–27 days, >27 days). The presence of diabetes mellitus (E08–E11, E13, E14) and myocardial infarction (I21) was identified if the subjects had the diagnostic codes before or at the index stroke.[1,2] Diabetes mellitus was recognized as relevant if the subjects received anti-diabetic prescriptions (sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, or insulin) with the diagnostic code.[3] According to year of the index stroke, patients were grouped into three strata: 2002–2005, 2006–2009, and 2010–2013.

Statistical analyses

According to antihypertensive medication adherence (poor, intermediate, and good) during the first 3 months after hemorrhagic stroke, we compared the characteristics using the Jonckheere trend test for age and the chi-square for trend test for other categorical characteristics. The event-free survival plot with the time-dependent variable of adherence to antihypertensive medication was illustrated using the method of Simon and Makuch, and the survival curves were compared by the Mantel-Byar test.[4,5] Hazard ratio and 95% confidence interval for primary outcome were calculated based on time-dependent Cox proportional hazard regression analyses. In the multivariate Cox regression, adherence to antihypertensive medication was treated as time-dependent variable and adjustments were performed for sex, age (as continuous variable), type of hemorrhagic stroke (intracerebral hemorrhage or subarachnoid hemorrhage), presence of diabetes mellitus, myocardial infarction, length of hospital stay (<16 days, 16–27 days, >27 days), household income (low, middle, high), and year of index stroke strata, which were treated as time-fixed covariates. For secondary outcome analyses, we constructed individual Cox regression models for recurrent stroke, myocardial infarction, cardiovascular and all-cause mortality as events of interest. The proportional hazards assumption for the adherence to antihypertensive medication was tested by calculating the Schoenfeld residuals, which was found to be satisfactory. The data manipulation and statistical analyses were performed with PostgreSQL version 10.1 (The PostgreSQL Global Development Group; https://www.postgresql.org/) and R software version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). A two-sided *P* value <0.05 was considered statistically significant.

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Table S1. Example of calculation of proportion of day covered to antihypertensive medication in everyday of follow-up

Patient ID	Day	prescription of antihypertensive medication	covered by antihypertensive medication at the day	PDC_{fu}	Classification of PDC_{fu}	comment
1	1		no	0/1	poor	index date, admission date for index hemorrhagic stroke
1	2		no	0/2	poor	
1	3		no	0/3	poor	
1	4		no	0/4	poor	
1	5		no	0/5	poor	
1	6		no	0/6	poor	
1	7	amlodipine * 30 days	yes	1/7	poor	1st prescription for 30 days
1	8		yes	2/8	poor	
⋮	⋮		⋮	⋮	⋮	
1	25		yes	19/25	intermediate	
1	26		yes	20/26	intermediate	
⋮	⋮		⋮	⋮	⋮	
1	35		yes	29/35	good	
1	36		yes	30/36	good	end of 1st prescription
1	37		no	30/37	good	
1	38		no	30/38	intermediate	
1	39		no	30/39	intermediate	
⋮	⋮		⋮	⋮	⋮	
1	45		no	30/45	intermediate	
1	46	amlodipine * 28 days, olmesartan * 28 days	yes	31/46	intermediate	2nd prescription for 28 days
1	47		yes	32/47	intermediate	
1	48		yes	33/48	intermediate	
⋮	⋮		⋮	⋮	⋮	
1	72		yes	57/72	intermediate	
1	73		yes	58/73	intermediate	end of 2st prescription
1	74		no	58/74	intermediate	
1	75		no	58/75	intermediate	
1	76		no	58/76	intermediate	
1	77		no	58/77	intermediate	
1	78	amlodipine * 28 days,	yes	59/78	intermediate	3rd prescription for 28 days

		olmesartan * 28 days			
1	79		yes	60/79	intermediate	
⋮	⋮		⋮	⋮	⋮	
1	89		yes	70/89	intermediate	
1	90		yes	71/90	intermediate	PDC for the first 3-month after hemorrhagic stroke is 71/90=0.789 (PDC_{3month})
1	91		yes	72/91	intermediate	
1	92		yes	73/92	intermediate	
1	93		yes	74/93	intermediate	
1	94		yes	75/94	intermediate	
1	95		yes	76/95	intermediate	
1	96		yes	77/96	good	
⋮	⋮		⋮	⋮	⋮	
1	104		yes	85/104	good	
1	105		yes	86/105	good	end of 3rd prescription
1	106		no	86/106	good	
⋮	⋮		⋮	⋮	⋮	

PDC_{fu} indicates proportion of days covered to antihypertensive medication over the period of follow-up.

Table S2. Comparison of characteristics in adherence to antihypertensive mediation during the first 3-month after acute hemorrhagic stroke

Variable	Adherence to antihypertensive medication over the first 3-month after acute hemorrhagic stroke			*P*-value*
	Poor: PDC_{3month} <40%, N=534	Intermediate: PDC_{3month} 40–80%, N=412	Good: PDC_{3month} >80%, N=926	
Type of stroke				<0.001
ICH	333 (62.4)	279 (67.7)	742 (80.1)	
SAH	201 (37.6)	133 (32.3)	184 (19.9)	
Sex, male	263 (49.3)	176 (42.7)	455 (49.1)	0.796
Age	60-64 [45-49; 70-74]	60-64 [50-54; 70-74]	60-64 [50-54; 70-74]	0.676
Diabetes mellitus	95 (17.8)	73 (17.7)	202 (21.8)	0.046
Myocardial infarction	36 (6.7)	31 (7.5)	58 (6.3)	0.652
Length of hospital stay, day				<0.001
<16 days	219 (41.0)	171 (41.5)	296 (32.0)	
16–27 days	180 (33.7)	127 (30.8)	287 (31.0)	
>27 days	135 (25.3)	114 (27.7)	343 (37.0)	
Household income				0.439
low	155 (29.0)	113 (27.4)	254 (27.4)	
middle	182 (34.1)	139 (33.7)	312 (33.7)	
high	197 (36.9)	160 (38.8)	360 (38.9)	
Year of admission				0.050
2002–2005	196 (36.7)	165 (40.0)	324 (35.0)	
2006–2009	185 (34.6)	134 (32.5)	282 (30.5)	
2010–2013	153 (28.7)	113 (27.4)	320 (34.6)	

Data are number (%) or median [interquartile range].

* P-value for trend across the patient groups by adherence to antihypertensive medication (poor, intermediate, and good).

PDC_{3month}, proportion of days covered by antihypertensive medication over 3-month after acute hemorrhagic stroke. ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

Table S3. Effects of adherence to antihypertensive medication after hemorrhagic stroke considering adherence to CCB and ACEI/ARB

Adherence to antihypertensive medication	Crude HR [95% CI]			Adjusted HR [95% CI]*		
	All, N=1872	ICH, N=1354	SAH, N=518	All, N=1872	ICH, N=1354	SAH, N=518
Poor (PDC_{fu} <40%)†	1.48 [1.14–1.92]‡	1.60 [1.19–2.16]‡	1.18 [0.71–1.96]	1.46 [1.14–1.89]‡	1.58 [1.18–2.11]‡	1.17 [0.71–1.92]
Intermediate (PDC_{fu} 40–80%)†	1.38 [1.05–1.82]‡	1.44 [1.05–1.97]‡	0.80 [0.42–1.53]	1.27 [0.97–1.68]	1.45 [1.07–1.97]‡	0.69 [0.35–1.33]
Good (PDC_{fu} >80%)†						
PDC_{fu} by CCB >0.8 and PDC_{fu} by ACEI/ARB >0.8	0.71 [0.48–1.05]	0.68 [0.45–1.04]	0.47 [0.14–1.61]	0.70 [0.47–1.03]	0.78 [0.51–1.19]	0.48 [0.13–1.69]
PDC_{fu} by CCB >0.8 and PDC_{fu} by ACEI/ARB ≤0.8	Ref	Ref	Ref	Ref	Ref	Ref
PDC_{fu} by CCB ≤0.8 and PDC_{fu} by ACEI/ARB >0.8	0.75 [0.53–1.07]	0.72 [0.49–1.07]	0.69 [0.30–1.59]	0.69 [0.49–0.98]‡	0.74 [0.50–1.10]	0.59 [0.25–1.37]
PDC_{fu} by CCB ≤0.8 and PDC_{fu} by ACEI/ARB ≤0.8	1.06 [0.73–1.52]	1.14 [0.77–1.70]	0.39 [0.12–1.33]	0.83 [0.58–1.20]	1.00 [0.67–1.48]	0.28 [0.08–0.92]‡

Data are derived by multivariate Cox proportional hazard regression model treating adherence to antihypertensive medication as time-dependent variable.
*adjusted for type of hemorrhagic stroke, sex, age, diabetes mellitus, prior myocardial infarction, household income, length of hospital stay, year of index hemorrhagic stroke.
†based on proportion of days covered to any antihypertensive medication during the follow-up period.
‡statistically significant compared to 'PDC_{fu} by CCB >0.8 and PDC_{fu} by ACEI/ARB ≤0.8'.
PDC_{fu} indicates proportion of days covered to any antihypertensive medication or the specific class of antihypertensive medication during the follow-up period; ACEI/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker; CCB, calcium channel blocker.

Table S4. Secondary outcome analysis according to the adherence to antihypertensive medication after hemorrhagic stroke

Secondary outcome, number of patients with the event during follow-up	Adjusted HR [95% CI]*			
	Recurrent stroke, n=233	Myocardial infarction, n=12	All-cause mortality, n=471	Cardiovascular mortality†, n=302
Adherence to antihypertensive medication				
Poor (PDC_{fu} <40%)	1.30 [0.96–1.75]	0.64 [0.16–2.64]	2.25 [1.80–2.80]	2.44 [1.86–3.20]
Intermediate (PDC_{fu} 40–80%)	1.21 [0.86–1.69]	0.97 [0.26–3.70]	1.79 [1.40–2.30]	1.75 [1.27–2.40]
Good (PDC_{fu} >80%)	Ref	Ref	Ref	Ref

Data are derived by multivariate Cox proportional hazard regression model treating adherence to antihypertensive medication as time-dependent variable.
*adjusted for type of hemorrhagic stroke, sex, age, diabetes mellitus, prior myocardial infarction, household income, length of hospital stay, and year of index hemorrhagic stroke.
†defined as mortality cases who had codes of 'I00–I99' as cause of death in the death statistics.
PDC_{fu} indicates proportion of days covered by antihypertensive medication over the period of follow-up; HR, hazard ratio; CI, confidence interval.