Choices for long-term hypertensive control in patients after first-ever hemorrhagic stroke: a nationwide cohort study

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Abstract

Background: To compare the long-term clinical outcomes of different antihypertensive drugs in stable patients after acute hemorrhagic stroke (HS).

Methods: From January 2001 to December 2013, patients with first-ever primary HS were identified in the National Health Insurance Research Database, Taiwan. Patients with traumatic intracerebral hemorrhage and secondary HS were excluded. Those with first-ever HS were recruited and classified into three groups: (1) angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB); (2) calcium channel blocker (CCB); and (3) other antihypertensive drugs (comparison) groups. Propensity score matching was used to balance the distribution of baseline characteristics, stroke severity, and medications between any two of the three groups. A validation study was performed using the databank of the Stroke Registry in Chang-Gung Healthcare System to reduce the bias. Primary outcomes were recurrent HS, ischemic stroke, any stroke, and all-cause mortality.

Results: Compared to the comparison group, the ACEI/ARB group [35.4% *versus* 39.3%; hazard ratio (HR), 0.84; 95% confidence interval (CI), 0.74–0.95] and CCB group (33.0% *versus* 41.9%; HR, 0.72; 95% CI, 0.64–0.81) had a lower risk of all-cause mortality during long-term follow up. The CCB group had a similar risk of all-cause mortality to the ACEI/ARB group. Risks of recurrent HS, ischemic stroke, or any stroke were not different between the study groups.

Conclusions: Antihypertensive drug class could be important to long-term outcomes in HS patients in addition to the target control of blood pressure. Both ACEIs/ARBs and CCBs are associated with lower risks of all-cause mortality. Our results may be applied to inform future research on hypertensive control in HS patients.

Keywords: angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, hemorrhagic stroke, hypertension

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Introduction

Stroke is the leading cause of death worldwide. Both ischemic stroke (IS) and hemorrhagic stroke (HS) survivors have high mortality rates during long-term follow up. Our previous study showed that in IS survivors, recurrent IS, cancer-related death, and cardiac disease are the main causes of death.[1] However, in HS survivors, preventing recurrent HS is the most effective method to reduce mortality.[1] To prevent recurrent HS, blood pressure (BP) should be well and intensively controlled.[2–5] However, it remains uncertain whether there were pleiotropic effects in different classes of antihypertensive drugs on HS patients. Although angiotensin-converting enzyme inhibitors (ACEIs) with diuretics are reported to be the treatment of choice for secondary stroke prevention,[5] the results were mainly

derived from IS patients and may be less applicable to HS patients.

Asia has an ideal population to study HS due to the population's characteristic of having a high proportion of small vessel disease (SVD), which accounts for the increased frequency of HS and lacunar infarction.[6,7] ACEIs and angiotensin receptor blockers (ARBs) are usually used as the first-line drugs for hypertensive patients.[5,8,9] Calcium channel blockers (CCBs) may have some roles in SVD through their effects on voltage-gated calcium channels, but this assumption lacks supporting sufficient clinical studies.[10,11] Until now, few outcome studies focused on direct comparison among different classes of antihypertensive drugs in HS patients. Therefore, the latest guidelines cannot give conclusive recommendations on the choice of antihypertensive drug class in HS patients.[5,12,13] The present study compared the long-term outcomes of CCBs and ACEIs/ARBs with other classes of antihypertensive drugs in stable patients after their first-ever HS. We hypothesized that in hypertension control, the class of antihypertensive drugs could be associated with additional benefits beyond the target control of BP in HS patients.

Methods

Patient enrollment and inclusion/exclusion criteria

This study was an open prospective nationwide cohort study including all patients admitted due to HS in the National Health Insurance Research Database (NHIRD) between January 1, 2001 and December 31, 2013. The NHIRD prospectively records the data submitted to the National Health Insurance (NHI) program, which covers more than 99% of the population in Taiwan. Diagnoses are registered using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and are routinely monitored by the NHI Bureau.[14] The patients of interest were first-ever primary HS survivors. In total, 114,219 hospitalized patients with a primary diagnosis of HS in the NHIRD (ICD-9-CM code 431) were initially included for analysis. We excluded patients with traumatic intracerebral hemorrhage (ICD-9-CM code 853) or with a previous history of HS including intracerebral hemorrhage and subarachnoid hemorrhage. We also excluded patients assumed to be associated with secondary HS if they also had a concurrent diagnosis of venous sinus thrombosis, cerebral aneurysm or arteriovenous fistula, non-aneurysmal subarachnoid hemorrhage, or non-traumatic subdural hemorrhage. In order to validate the diagnostic accuracy of a first-ever HS in NHIRD, we compared the data of patients with the primary diagnosis of HS from both the NHIRD and the Stroke Registry in Chang Gung Healthcare System (SRICHS) from 2009 to 2013.[15] The details are provided in Supplemental Figure 1.

According to our previous study,[1] more than half of the mortality in HS patients occurred within the first month after stroke onset. Drug switching or discontinuation occurs more commonly within the first 180 days after the start of medication.[16] These factors may lead to misinterpretation of the correlations between antihypertensive drugs and clinical outcomes. To study HS patients in the stable phase, we excluded those patients who died during the index hospitalization and those who developed HS or had composite cardiovascular outcomes within 180 days after the index hospitalization. We also excluded those patients who had follow up of fewer than 180 days and who did not receive any antihypertensive agents within 180 days after the index hospitalization (Figure 1). The Ethics Institutional Review Board of Chang Gung Memorial Hospital approved this study (approval number: 201601164B0). Because the enrolled patients cannot be identified in this claims database study, informed consent was waived by our Ethics Institutional Review Board.

Exposure to study drugs

The eligible patients were divided into three groups according to the main antihypertensive drugs prescribed during the follow-up period: (1) ACEI/ARB, (2) CCB, and (3) comparison (other antihypertensive medications) groups. To ensure the consistent use of study drugs in each group, patients were excluded if they took any CCB in the ACEI/ARB group, any ACEI/ARB in the CCB group, and any ACEI/ARB or CCB in the comparison group for even 1 day during a 2-year exposure period. Patients were also excluded if they received the study drug for fewer than 60 days. Since BP levels were not recorded in the NHIRD, the add-on antihypertensive drugs and the number of antihypertensive drug classes within a 2-year exposure period were adjusted to minimize the bias related to the different levels of BP. Also, with the linkage between SRICHS and

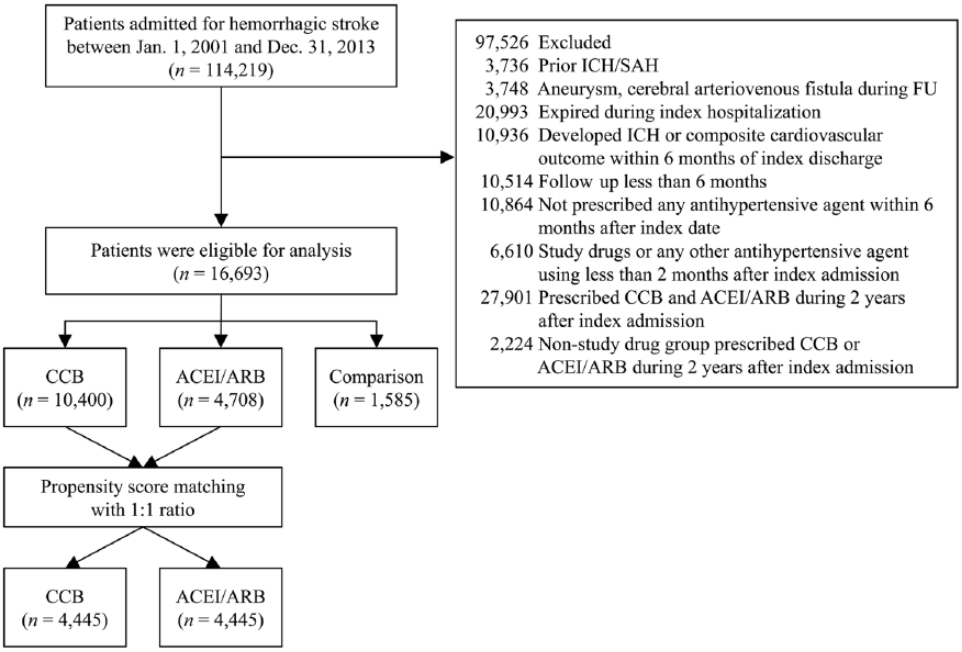

Figure 1. Flow chart of the recruitment of the study patients. Patients with their first-ever hemorrhagic stroke are included after relevant exclusions and then further divided into three groups according to the prescribed antihypertensive therapy.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; FU, follow up; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

NHIRD, the mean BPs at admission in the SRICHS were used to represent the baseline BP levels of the matched patients in the three study groups. The medication possession ratio was calculated to assess the adherence of the study drug in each group. The index hospitalization was defined as the first hospitalization due to HS throughout the study period. The follow-up period was calculated from the admission day of index hospitalization to the day of death or until December 31, 2013, whichever occurred first.

Outcomes and covariate measurements

Medications and ICD-9-CM diagnosis codes during the index hospitalization were used to represent the baseline medications and comorbidities. The diagnosis code in at least two consecutive outpatient follow-up visits or in one inpatient record in the previous year of the index hospitalization was used to confirm the comorbidity. In addition, the diagnoses of hemodialysis and cancer were further verified using catastrophic illness certificates (Supplemental Table 1). The prescribed medications were confirmed using Anatomical Therapeutic Chemical codes (Supplemental Table 2). Over 99% of the population and hospitals in Taiwan are enrolled in the NHI program. Therefore, almost all the major outcomes that occurred between January 1, 2001 and December 31, 2013 were recorded. The primary outcomes were defined as admission due to recurrent HS, IS, or any stroke, all-cause mortality, and composite end-points. The composite end-points included IS, HS, and all-cause mortality. Recurrent HS was identified by hospitalization with ICD-9-CM code 431 during the follow-up period. IS was identified by hospitalization with ICD-9-CM codes 433–435, except 433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 434.90, 434.00, 434.10, and 434.90 during the follow-up period. The secondary end-points included cardiovascular death, hemodialysis, and myocardial infarction (MI). The definitions of MI, cardiovascular death, and all-cause mortality were the same as those used in the NHIRD study (Supplemental Table 1).[17]

Statistical analysis

We performed propensity score matching (PSM) to balance the distribution of baseline

characteristics, the numbers of antihypertensive drug class used at baseline, and the use of non-antihypertensive medications between any two study groups. We also included the estimated National Institutes of Health Stroke Scale (NIHSS) score as a covariate when generating propensity score.[18] We adopted the greedy nearest-neighbor matching algorithm and set the caliper as 0.2 times the standard deviation of the propensity score. To minimize bias of treatment effect estimation, we used a 1:1 matching ratio.[19]

The baseline characteristics were initially compared using one-way analysis of variance for continuous variable and the Chi-square test for categorical variable before PSM. These data were further compared between any two of the three groups using the two-sample *t* test for continuous variables and the Chi-square test for categorical variables after PSM. The risk of time to event between any two of the three groups after PSM was compared using a Cox proportional hazard model in which the study group was the independent variable and propensity score was treated as a covariate. The cumulative incidence comparing the time to all-cause mortality, recurrent HS, and IS between any two of the three groups was depicted using the adjusted survival curves in the multivariable Cox model. All data analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Statistical significance was set at $p < 0.05$.

Results

Study patients

Between January 1, 2001 and December 31, 2013, a total of 699,291 patients admitted due to stroke (ICD-9-CM codes 430–437) were available in the NHIRD. In total, 114,219 patients who were admitted due to a HS (ICD-9-CM code 431) were initially included. Overall, 16,693 first-ever HS patients were confirmed eligible for analysis based on the inclusion/exclusion criteria. A total of 2343 and 234 from the 114,219 HS and 16,693 first-ever HS patients, respectively, were matched with the SRICHS for validation. The positive predictive values of HS and first-ever HS diagnoses in this study were 97.98% and 90.54%, respectively (Supplemental Figure 1). There were 10,400 patients in the CCB group, 4708 patients in the ACEI/ARB group, and 1585 patients in the comparison group (Figure 1).

Baseline characteristics (Table 1)

Before PSM, the ACEI/ARB group had a higher frequency of male patients, diabetes mellitus (DM), and dyslipidemia than the other two groups. The CCB group had a lower prevalence of previous MI, previous IS, coronary artery disease, atrial fibrillation (AF), DM, dyslipidemia, and previous antiplatelet or anticoagulant therapy than the other two groups. The proportions of patients confined to a single class of antihypertensive drug within 2 years were 49.8%, 49.2%, and 59.6% in the CCB, ACEI/ARB, and comparison groups ($p < 0.001$), respectively, compared to 42.2%, 42.5%, and 23.8% in those using more than two classes of antihypertensive drugs. The proportions of patients receiving non-study medications before PSM were recorded (Supplemental Table 2). The medication possession ratios of CCBs, ACEIs/ARBs, and other antihypertensive drugs were 83.7%, 84.5%, and 87.1% in the CCB, ACEI/ARB, and comparison groups during the 2-year follow-up period. Comparisons of the baseline characteristics and medications after PSM between any two of the three groups are shown in Supplemental Tables 3–5.

Primary outcomes

The primary outcomes were compared between any two of the three study groups after PSM. Compared to the comparison group, the ACEI/ARB group had a lower risk of all-cause mortality at 2-year [ACEI/ARB *versus* comparison: 12.6% *versus* 16.3%; hazard ratio (HR), 0.74; 95% confidence interval (CI), 0.61–0.91], 5-year (26.0% *versus* 30.1%; HR, 0.81; 95% CI, 0.70–0.93), and the last follow up (35.4% *versus* 39.3%; HR, 0.84; 95% CI, 0.74–0.95) (Table 2). The CCB group also had a lower risk of all-cause mortality at 2-year (CCB *versus* comparison: 11.1% *versus* 16.8%; HR, 0.63; 95% CI, 0.52–0.77), 5-year (24.2% *versus* 32.3%; HR, 0.69; 95% CI, 0.60–0.79), and the last follow up (33.0% *versus* 41.9%; HR, 0.72; 95% CI, 0.64–0.81) (Table 3). The incidence rates of HS and IS were similar among the ACEI/ARB, CCB, and comparison groups.

The incidence rates of all-cause mortality, HS, IS, any stroke, and primary composite end-points were not significantly different between the ACEI/ARB and CCB groups throughout the follow-up period (Table 4). The mean follow-up period was 4.5 ± 3.3 and 4.6 ± 3.4 years in the

Table 1. Baseline clinical characteristics of the study patients before propensity score matching.

Characteristics	CCB (n = 10,400)	ACEI/ARB (n = 4708)	Comparison (n = 1585)	p
Age (years)	63.4 ± 13.2	63.2 ± 13.6	64.9 ± 14.7	<0.001
<40	342 (3.3)	197 (4.2)	71 (4.5)	<0.001
40–75	7813 (75.1)	3421 (72.7)	1045 (65.9)	
>75	2245 (21.6)	1090 (23.2)	469 (29.6)	
Gender				0.002
Male	6372 (61.3)	3026 (64.3)	992 (62.6)	
Female	4028 (38.7)	1682 (35.7)	593 (37.4)	
Previous myocardial infarction	81 (0.8)	90 (1.9)	31 (2.0)	<0.001
Previous ischemic stroke	422 (4.1)	210 (4.5)	91 (5.7)	0.008
Previous antiplatelet use	2010 (19.3)	1195 (25.4)	382 (24.1)	<0.001
Previous anticoagulant use	100 (1.0)	126 (2.7)	79 (5.0)	<0.001
Comorbidity				
Coronary artery disease	874 (8.4)	653 (13.9)	239 (15.1)	<0.001
Chronic kidney disease	278 (2.7)	114 (2.4)	39 (2.5)	0.632
Hemodialysis	109 (1.0)	40 (0.8)	9 (0.6)	0.133
Chronic obstructive pulmonary disease	541 (5.2)	287 (6.1)	172 (10.9)	<0.001
Atrial fibrillation	176 (1.7)	202 (4.3)	78 (4.9)	<0.001
Diabetes mellitus	1667 (16.0)	1183 (25.1)	333 (21.0)	<0.001
Dyslipidemia	1136 (10.9)	773 (16.4)	189 (11.9)	<0.001
Malignancy	335 (3.2)	163 (3.5)	75 (4.7)	0.009
NIHSS	15.4 ± 6.9	14.1 ± 7.0	15.7 ± 7.3	<0.001
NIHSS group				<0.001
⩽5	920 (8.8)	627 (13.3)	175 (11.0)	
6–13	3308 (31.8)	1678 (35.6)	436 (27.5)	
>13	6172 (59.3)	2403 (51.0)	974 (61.5)	
Follow-up years	5.3 ± 3.4	4.4 ± 3.3	4.7 ± 3.4	<0.001
Baseline antihypertensive drugs				
ACEI/ARB	0 (0)	100 (100)	0 (0)	<0.001

(Continued)

Table 1. (Continued)

Characteristics	CCB (n = 10,400)	ACEI/ARB (n = 4708)	Comparison (n = 1585)	p
CCB	100 (0)	0 (0)	0 (0)	<0.001
Alpha-blocker	874 (8.4)	417 (8.9)	244 (15.4)	<0.001
Beta-blocker	3559 (34.2)	1578 (33.5)	1018 (64.2)	<0.001
Thiazide	693 (6.7)	383 (8.1)	158 (10.0)	<0.001
Loop diuretics	833 (8.0)	501 (10.6)	463 (29.2)	<0.001
Spironolactone	114 (1.1)	97 (2.1)	188 (11.9)	<0.001
Others	330 (3.2)	126 (2.7)	44 (2.8)	0.218
Numbers of antihypertensive drug types used at baseline				<0.001
1	5363 (51.6)	2375 (50.4)	1138 (71.8)	
2	3879 (37.3)	1706 (36.2)	371 (23.4)	
⩾3	1158 (11.1)	627 (13.3)	76 (4.8)	
Add-on antihypertensive drugs within two years				
Antihypertensive drug not of interest				
Beta-blocker	546 (5.3)	256 (5.4)	29 (1.8)	<0.001
Alpha-blocker	209 (2.0)	93 (2.0)	14 (0.9)	0.008
Thiazide	255 (2.5)	116 (2.5)	24 (1.5)	0.064
Loop diuretics	409 (3.9)	205 (4.4)	84 (5.3)	0.032
Spironolactone	84 (0.8)	58 (1.2)	33 (2.1)	<0.001
Other	99 (1.0)	31 (0.7)	8 (0.5)	0.060
Numbers of antihypertensive drug types used at two years				<0.001
0	837 (8.1)	393 (8.4)	264 (16.7)	
1	5177 (49.8)	2316 (49.2)	944 (59.6)	
⩾2	4386 (42.2)	1999 (42.5)	377 (23.8)	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NIHSS, National Institutes of Health Stroke Scale.

ACEI/ARB and CCB groups (p = 0.77). The multivariate adjusted survival curves showed lower trends of all-cause mortality in the ACEI/ARB and CCB groups compared to the comparison group ($p < 0.05$). Compared to the ACEI/ARB group, the CCB group showed a similar trend of all-cause mortality throughout the follow-up period (Figure 2). The survival curves of IS and HS between the study groups are shown in Supplemental Figures 2 and 3.

Secondary outcomes

The ACEI/ARB group had a lower risk of new-onset hemodialysis compared to the CCB group at the last follow up (0.7% *versus* 1.5%; HR,

Table 2. Primary outcomes in the ACEI/ARB and comparison groups after propensity score matching.

Outcome	ACEI/ARB (n = 1386)	Comparison (n = 1386)	ACEI/ARB *versus* comparison	
			HR (95% CI)†	*p*
2-year follow up				
All-cause mortality	175 (12.6)	226 (16.3)	0.74 (0.61, 0.91)	0.003
Any stroke#	107 (7.7)	108 (7.8)	0.95 (0.73, 1.24)	0.704
Hemorrhagic stroke	47 (3.4)	49 (3.5)	0.92 (0.62, 1.38)	0.699
Ischemic stroke	66 (4.8)	66 (4.8)	0.96 (0.68, 1.35)	0.813
Primary composite end-point§	261 (18.8)	308 (22.2)	0.81 (0.69, 0.96)	0.013
5-year follow up				
All-cause mortality	360 (26.0)	417 (30.1)	0.81 (0.70, 0.93)	0.003
Any stroke#	234 (16.9)	217 (15.7)	1.01 (0.84, 1.21)	0.933
Hemorrhagic stroke	112 (8.1)	103 (7.4)	1.02 (0.78, 1.33)	0.902
Ischemic stroke	147 (10.6)	137 (9.9)	1.01 (0.80, 1.27)	0.949
Primary composite end-point§	523 (37.7)	554 (40.0)	0.88 (0.78, 0.99)	0.037
At the last follow up				
All-cause mortality	491 (35.4)	545 (39.3)	0.84 (0.74, 0.95)	0.005
Any stroke#	295 (21.3)	274 (19.8)	1.02 (0.86, 1.20)	0.849
Hemorrhagic stroke	143 (10.3)	142 (10.2)	0.95 (0.75, 1.19)	0.642
Ischemic stroke	185 (13.3)	175 (12.6)	1.000 (0.81, 1.23)	0.999
Primary composite end-point§	666 (48.1)	678 (48.9)	0.92 (0.83, 1.03)	0.133

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio.
§Any one of all-cause mortality, hemorrhagic stroke, and ischemic stroke.
#Either one of hemorrhagic or ischemic stroke.
†Propensity score was additionally treated as a covariate in the model.

0.42; 95% CI, 0.27–0.65) (Supplemental Tables 6–8).

Discussion

In addition to the target control of BP, our results demonstrate that class selection of antihypertensive drugs may also be important in HS patients. Reduction of mortality is the major goal of antihypertensive treatment, and our results show both ACEI-/ARB- and CCB-based regimens were associated with lower risks of all-cause mortality compared to other drugs in HS patients. ACEIs/ARBs are usually the drug of choice in hypertensive patients,[5,8,9] and combination therapy with ACEIs and CCBs is reported to have better protective effects than other regimens.[8,20] Our finding that CCBs have an advantage in HS patients has rarely been studied before, and our results suggest that CCBs could also be used as a priority in HS survivors.

Renin-angiotensin system inhibitors (RASI), including ACEIs and ARBs, can effectively reduce cardiovascular mortality, especially in patients with heart diseases.[21] Since coronary artery disease and IS share similar risk factors, IS patients may also be at risk of cardiovascular mortality,

Table 3. Primary outcomes in the CCB and comparison groups after propensity score matching.

Outcome	CCB ($n = 1502$)	Comparison ($n = 1502$)	CCB *versus* comparison	
			HR (95% CI)†	*p*
2-year follow up				
All-cause mortality	167 (11.1)	253 (16.8)	0.63 (0.52, 0.77)	<0.001
Any stroke#	116 (7.7)	118 (7.9)	0.95 (0.73, 1.22)	0.665
Hemorrhagic stroke	51 (3.4)	53 (3.5)	0.92 (0.63, 1.36)	0.685
Ischemic stroke	73 (4.9)	71 (4.7)	0.99 (0.72, 1.38)	0.959
Primary composite end-point§	263 (17.5)	342 (22.8)	0.74 (0.63, 0.87)	<0.001
5-year follow up				
All-cause mortality	363 (24.2)	485 (32.3)	0.69 (0.60, 0.79)	<0.001
Any stroke#	241 (16.0)	235 (15.6)	0.95 (0.79, 1.13)	0.557
Hemorrhagic stroke	115 (7.7)	111 (7.4)	0.96 (0.74, 1.24)	0.741
Ischemic stroke	158 (10.5)	146 (9.7)	1.001 (0.80, 1.25)	0.993
Primary composite end-point§	528 (35.2)	627 (41.7)	0.78 (0.69, 0.88)	<0.001
At the last follow up				
All-cause mortality	495 (33.0)	629 (41.9)	0.72 (0.64, 0.81)	<0.001
Any stroke#	323 (21.5)	296 (19.7)	1.002 (0.86, 1.17)	0.979
Hemorrhagic stroke	159 (10.6)	151 (10.1)	0.96 (0.77, 1.20)	0.743
Ischemic stroke	222 (14.8)	187 (12.5)	1.09 (0.90, 1.33)	0.373
Primary composite end-point§	681 (45.3)	767 (51.1)	0.82 (0.74, 0.91)	<0.001

CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.
§Any one of all-cause mortality, hemorrhagic stroke, and ischemic stroke.
#Either one of hemorrhagic or ischemic stroke.
†Propensity score was additionally treated as a covariate in the model.

particularly the IS subtypes of cardioembolic stroke and large artery disease as seen in our previous study.[1] It is reported that RASI could be beneficial to IS patients,[8] but the benefits to HS patients are undetermined due to HS patients being infrequently enrolled in the previous studies.[8,20,21] Although RASIs were found to have benefits in animal models with HS,[22] the Scandinavian Candesartan Acute Stroke Trial, which used candesartan in 144 HS patients, only showed conflicting results with possibly harmful effects in the acute phase but neutral effects in the following 6 months.[23,24] Moreover, risk factor controls with benefits on IS patients may not show identical effects on HS patients.[25,26] Nevertheless, our study revealed that in HS patients the ACEI/ARB group had a 4% reduction of overall mortality compared to the comparison group, which was close to the previous studies focusing on all hypertensive patients.[27,28] Similar to the report in a recent meta-analysis,[29] our study also suggested that besides lowering BP, the ACEI/ARB group may have pleiotropic effects which result in a better clinical outcome compared to other antihypertensive drugs in HS patients. Our results could be of value because we demonstrated the potential benefits with regards to the long-term use of RASI in patients with HS.

Table 4. Primary outcomes in the ACEI/ARB and CCB groups after propensity score matching.

Outcome	ACEI/ARB ($n = 4445$)	CCB ($n = 4445$)	ACEI/ARB *versus* CCB	
			HR (95% CI)†	*p*
2-year follow up				
All-cause mortality	347 (7.8)	344 (7.7)	1.01 (0.87, 1.17)	0.940
Any stroke#	316 (7.1)	295 (6.6)	1.07 (0.91, 1.26)	0.397
Hemorrhagic stroke	150 (3.4)	134 (3.0)	1.12 (0.89, 1.41)	0.343
Ischemic stroke	186 (4.2)	185 (4.2)	1.002 (0.82, 1.23)	0.987
Primary composite end-point§	603 (13.6)	579 (13.0)	1.04 (0.93, 1.17)	0.480
5-year follow up				
All-cause mortality	726 (16.3)	715 (16.1)	1.01 (0.91, 1.12)	0.818
Any stroke#	621 (14.0)	595 (13.4)	1.04 (0.93, 1.17)	0.463
Hemorrhagic stroke	297 (6.7)	276 (6.2)	1.08 (0.91, 1.27)	0.383
Ischemic stroke	382 (8.6)	398 (9.0)	0.95 (0.83, 1.10)	0.508
Primary composite end-point§	1179 (26.5)	1145 (25.8)	1.03 (0.95, 1.12)	0.485
At the last follow up				
All-cause mortality	1015 (22.8)	982 (22.1)	1.05 (0.96, 1.15)	0.265
Any stroke#	802 (18.0)	803 (18.1)	1.01 (0.92, 1.12)	0.777
Hemorrhagic stroke	390 (8.8)	358 (8.1)	1.11 (0.96, 1.28)	0.160
Ischemic stroke	502 (11.3)	555 (12.5)	0.91 (0.81, 1.03)	0.140
Primary composite end-point§	1533 (34.5)	1518 (34.2)	1.03 (0.96, 1.10)	0.484

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.
§Any one of all-cause mortality, hemorrhagic stroke, and ischemic stroke.
#Either one of hemorrhagic or ischemic stroke.
†Propensity score was additionally treated as a covariate in the model.

The CCBs were noted to have better death-reduction results compared to beta-blockers in a systemic review.[30] However, the advantages of CCBs are not identical in patients with different comorbidities and very few clinical studies have focused on the use of CCBs in stable HS patients.[31] CCBs were noted to be superior to beta-blockers or diuretics in patients with metabolic syndrome or DM, but CCBs were reported only non-inferior to diuretics or beta-blockers in hypertensive patients with stable ischemic heart disease, AF, or chronic kidney disease.[5] Our HS population had a high frequency of DM and dyslipidemia but a low frequency of previous MI, previous IS, chronic kidney disease, and AF. Beta-blockers were used in 64.2% of patients in our comparison group. These factors may explain why our CCB group had a lower mortality rate compared to the comparison group. Of note, our study demonstrated that the benefits of CCBs and ACEIs/ARBs could be equivalent on the reduction of all-cause mortality in HS patients. Previous studies focusing on uncomplicated hypertensive patients have shown a similar trend.[32,33] Our results may further extend the potential benefits of CCBs when used in stable HS patients.

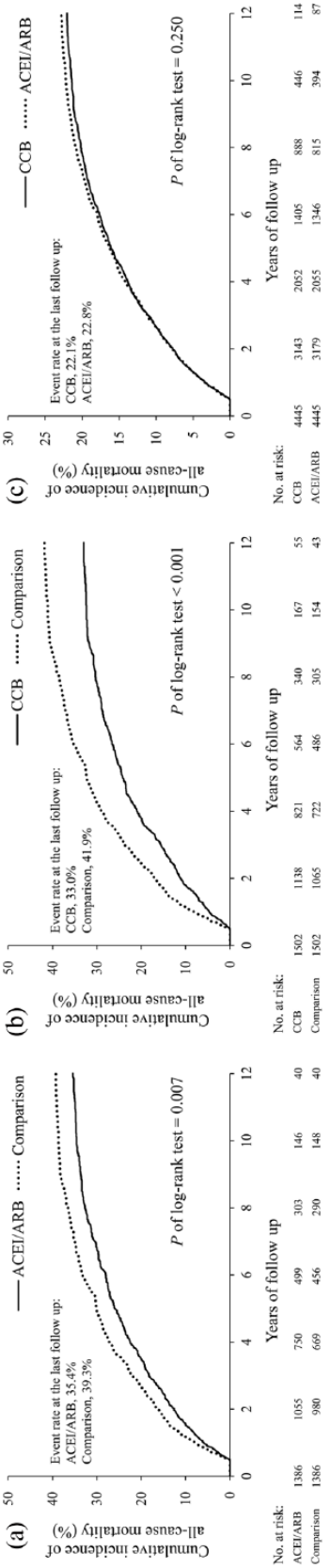

Figure 2. Comparisons of cumulative incidence of all-cause mortality between the study groups. The cumulative incidence comparing the time to all-cause mortality between the study groups. The multivariate adjusted survival curves of the ACEI/ARB (a) and CCB (b) groups show a lower trend of all-cause mortality compared to the comparison group. The CCB and ACEI/ARB groups have similar all-cause mortality throughout the follow-up period (c).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

A recent meta-analysis reported that ACEIs, ARBs, or CCBs were better than beta-blockers in stroke prevention.[34] Theoretically, ACEIs/ARBs may reduce recurrent strokes,[35] since ACEIs may influence plasminogen activator inhibitor-1 antigen and endothelial function,[35] and ARBs can mediate the protective effects against ischemic injury in brain tissue.[36] ARBs also prevent the progression of diabetes and new-onset AF, both of which are major risk factors for IS.[37] The risk of SVD may be associated with abnormal vascular tone,[38] and CCBs can act on the voltage-gated calcium channels which are known to participate in the control of vascular tone and associate with the contraction of cerebral vessels in hypertensive patients.[39] Therefore, CCBs are suggested to be effective in primary stroke prevention.[31,40,41] In a recent meta-analysis,[42] CCBs helped to reduce the risks of recurrent stroke. Nicardipine and labetalol are recommended for BP control during the acute stage of HS,[43] but there is a lack of evidence with regards to the most appropriate antihypertensive drugs in the stationary phase after acute HS.[13] Our HS patients taking ACEIs/ARBs or CCBs did not show better protective effects to the upcoming IS compared to other drugs. It is possible the frequency of upcoming IS might be low, or the follow-up period might not be long enough to show the clinical significance. Patients taking ACEIs/ARBs or CCBs were also not associated with significantly lower risks of recurrent HS in our study, which is similar to a recent meta-analysis focusing on the Asian population.[44] We assume that the target of lowering BP rather than the class effectiveness of antihypertensive drugs remains the key effect for the prevention of recurrent HS.

There are limitations in this study. First, the characteristics and locations of the hematoma in HS were reported to be associated with risks of recurrent HS and long-term prognosis.[45] However, the image reports were not available in the NHIRD. Nevertheless, we have excluded patients with ICD-9-CM codes of cerebral vascular abnormalities (e.g. aneurysm or arteriovenous malformation or fistula) to reduce the confounding effect from secondary HS. In the future, a nationwide cloud-based medical image-sharing platform with convolutional neural network analysis could be a potential solution.[46,47] Second, BP levels are not recorded in the NHIRD for the examination of BP targets and variability, which may be a major confounder for the evaluation of clinical outcomes. To reduce the bias of BP levels after antihypertensive treatment, we have balanced the medication possession ratios and the frequency

of patients taking more than two types of antihypertensive drugs at baseline and at 2 years. These factors have been reported as alternative parameters for the effectiveness evaluation of BP control.[48–50] Also, since these patients were enrolled between 2000 and 2013, the clinicians usually followed the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to control BP.[51] In Taiwan, all insurance claims will be scrutinized and peer-reviewed by medical reimbursement specialists. Physicians and their institutions will be accredited and penalized if they violate clinical guidelines. Third, stroke severity and outcome scores were not available in the NHIRD. However, a previous NHIRD study has established the "stroke severity index" to estimate "NIHSS scores" using treatment and intervention in the ICH admission.[18] In the present study, we used the stroke severity index,[18] alternative covariates, and medications to evaluate the disease severity of HS patients. The information on functional outcome, such as modified Rankin score, is also not available in the NHIRD. Since it has been reported that the modified Rankin score at discharge is correlated well with the NIHSS scores, we did not try to further adjust functional outcome.[18,52] Fourth, drug switching, combinations, and adherence are important confounders. In this study, adherence to the study drugs was controlled, and only the patients who used the study drugs continuously were included. PSM was also used for statistical adjustments. Fifth, ICD-9-CM may be coded incorrectly in the claim database. Our validation study using SRICHS supported the coding accuracy of the HS and first-ever HS patients in this study. Lastly, conclusions with regards to the causal effects of the study drugs may be limited in this observational study, and the generalizability of our findings to other ethnicities is undefined. Despite these limitations, our study is valuable because of the paucity of outcome studies regarding hypertensive controls in stable HS patients. Our hypothesis-driven cohort study with a large nationwide HS population, strictly controlled variables, and long-term follow up may be applied to inform well-designed randomized clinical trials to determine the most effective regimen of antihypertensive drugs for HS in the future.

Conclusion

In our study, ACEI-/ARB- and CCB-based regimens are both associated with lower risk of all-cause mortality during long-term follow up compared to other antihypertensive drugs. Our results suggest both ACEIs/ARBs and CCBs may be used as a priority in BP control in stable HS patients, and also inform future researches.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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