Association of Hypertension With Stroke Recurrence Depends on Ischemic Stroke Subtype

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Background and Purpose—The association between hypertension (HTN) and stroke recurrence is unclear, but may be influenced by different subtypes of stroke. This study aims to explore whether HTN contributes to the recurrence of certain subtypes of ischemic stroke (IS).

Methods—Data from the China National Stroke Registry was examined and 1-year follow-up data for stroke recurrence was analyzed. Trial of Org 10172 in Acute Stroke Treatment criteria was used to classify the subtypes of all IS. HTN was defined when resting blood pressure was ≥140/90 mm Hg on repeated measurements during hospitalization or a patient had been on antihypertensive medication. Recurrent stroke was defined as a new neurological deficit compatible to IS or intracerebral hemorrhage. The association between HTN and stroke recurrence in patients with different IS subtypes was analyzed by using univariable and multivariable logistic regression models.

Results—Of 11,560 patients with IS, 8,409 (72.7%) had HTN and 2,050 (17.7%) experienced a recurrent stroke within 1 year. Patients with HTN had an insignificantly higher stroke recurrence rate than those without (18.0% versus 17.0%; P = 0.21). After stratification by Trial of Org 10172 in Acute Stroke Treatment subtypes, multivariable analysis revealed a significant association between HTN and stroke recurrence in small-artery occlusion subtype (odds ratio, 1.52; 95% confidence interval, 1.03–2.31), but not in the other subtypes (large-artery atherosclerosis: odds ratio, 0.99; 95% confidence interval, 0.81–1.21; cardioembolic: odds ratio, 1.14; 95% confidence interval, 0.75–1.73; other: odds ratio, 0.88; 95% confidence interval, 0.71–1.09).

Conclusions—Our results showed that HTN is specifically related to the recurrent strokes in patients with small-vessel diseases, not other subtypes of IS. (Stroke. 2013;44:00-00.)

Key Words: hypertension ■ ischemic stroke ■ recurrent event

Known as a major risk factor contributing to the causes of ischemic stroke (IS), hypertension (HTN) has not been well studied as a risk factor for subsequent strokes.1–7 Because of methodological differences, previously published studies were vague on the association of HTN with the recurrence of strokes.8 HTN therefore may not contribute to subsequent strokes of different subtypes equally. This is because IS is a heterogeneous disease with variable pathogenesis.9 Most previous studies examined HTN as a potential risk factor for recurrent stroke among IS patients without distinguishing the initial IS subtypes.1–7 The aim of the current study was to assess the association between HTN and stroke recurrence in patients with different IS subtypes, as defined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.10

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brain computed tomography (CT) or MRI. All patients with acute IS were further classified according to the TOAST criteria: large-artery atherosclerosis (LAA), small-artery occlusion (SAO), cardioembolism (CE), stroke of other determined pathogenesis, and stroke of undetermined pathogenesis. Subtype classification was based on patient’s features combined with the results of 1 or more diagnostic tests, including brain imaging (CT and MRI), EKG, echocardiography (transesophageal or transthoracic), imaging of extracranial and intracranial arteries (carotid duplex, transcranial Doppler, CT angiography, magnetic resonance angiography, or digital subtraction angiography), and laboratory assessments for a prothrombotic state. At least 2 study neurologists from each participating hospital reviewed the clinical features and diagnostic tests results, and then gave the subtype classifications. These neurologists were trained centrally and the diagnostic criteria of subtype classifications were consistent across all participating hospitals: (1) Patients with LAA had clinical and brain imaging findings of either significant (≥50%) stenosis or occlusion of a major brain artery or branch cortical artery. Clinical findings included cerebral cortical impairment (e.g., aphasia, neglect, apraxia, anopia, restricted motor involvement) or brain stem or cerebellar dysfunction. Infarct areas were >1.5 cm in diameter on CT or MRI. (2) Patients with SAO had one of the traditional clinical lacunar syndromes (including pure motor stroke, pure sensorimotor stroke, pure sensory stroke, ataxic hemiparesis, or clumsy hand dysarthria) and did not have evidence of cerebral cortical dysfunction. Infarct areas were <1.5 cm in diameter on CT or MRI. A history of HTN or diabetes mellitus supports the clinical diagnosis. Evidence of cardiac sources of embolism was absent and large extracranial arteries had a stenosis of <50% in an ipsilateral artery. (3) Patients with CE had at least one cardiac source for an embolus, including rheumatic mitral valve disease, nonvalvular atrial fibrillation, sick sinus syndrome, recent myocardial infarction (<4 weeks), cardiac thrombus, valvular vegetation, akinetic left ventricular segment, atrial myxoma, dilated cardiomyopathy, prosthetic mitral or aortic valve, and paradoxical emboli. Clinical and brain imaging findings are similar to those described for LAA. The angiogram or ultrasonogram does not show significant (≥50%) stenosis or ulcerated plaques in the proximal large-artery supply. (4) Patients with stroke of other determined pathogenesis had rare causes of stroke, including nonatherosclerotic vasculopathies, hypercoagulable states, or hematoletic disorders. (5) Stroke of undetermined pathogenesis was defined when any of the following criteria were met: (a) no cause was found despite an extensive evaluation; (b) a most likely cause could not be determined because >1 plausible cause was found; or (c) undetermined pathogenesis attributable to incomplete evaluation. As there were a few patients in the stroke of other determined pathogenesis subtype (1.6%), these patients were combined with the stroke of undetermined pathogenesis subgroup and defined together as “Other.” Hence, patients with IS in this study were classified into 4 subtypes (LAA, SAO, CE, and “Other”).

HTN was defined when a patient’s blood pressure was ≥140/90 mmHg on repeated measurements during the hospitalization or patient was on antihypertensive medication. Other risk factors were defined as follows: history of stroke (defined as a medical chart-confirmed history of stroke, including IS, intracerebral hemorrhage, or subarachnoid hemorrhage), coronary heart disease (a reported history of myocardial infarction or cardiac surgery, or with a final diagnosis of myocardial infarction at discharge), atrial fibrillation (a reported history of atrial fibrillation, or diagnosed using the patient’s in-hospital EKG), diabetes mellitus (fasting blood glucose level ≥120 mg/dL, or use of antidiabetic drugs), dyslipidemia (total cholesterol measurement ≥240 mg/dL, high-density lipoprotein measurement <35 mg/dL, or use of lipid-lowering agents), current or previous smoking (defined as an individual who smoked at the time of stroke or had quit smoking within 1 year), and moderate or heavy drinking (≥2 standard alcoholic beverages consumed per day). Other clinical features included severity of stroke on admission (National Institutes of Health Stroke Scale score),13 and persistence with secondary prevention medication, including antithrombotic (antiplatelet or anticoagulation) agents and antihypertensive agents (including angiotensin-converting enzyme inhibitors).

Figure 1. Patient flow diagram. CE indicates cardioembolism; CNSR, China National Stroke Registry; HTN, hypertension; LAA, large-artery atherosclerosis; and SAO, small-artery occlusion.
inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, β-blockers, and other antihypertensives, including centrally acting adrenergics, peripherally acting antiadrenergics, and vasodilators). Persistence was calculated as the cumulative duration of taking medication divided by the length of the follow-up period. Persistence of ≥75% was defined as high and <75% was defined as low. Patients who did not take any medication during the follow-up period were defined as untreated. The detailed definition of persistence can be found in the online-only Data Supplement.

Recurrent stroke was defined as a new neurological deficit or a deterioration of the previous deficit that fits the definitions for ischemic or hemorrhagic stroke, not considered to be because of edema, hemorrhagic transformation, or intercurrent illness. At 3, 6, and 12 months after the incident stroke, patients or their relatives were asked whether they had new symptoms and experienced rehospitalization with a diagnosis of IS or intracerebral hemorrhage. Hospitals that admitted patients with recurrent strokes were contacted to verify the diagnosis. All recurrent events were based on clear documentation in medical records, and neurological deficits had lasted longer than 24 hours. If a patient died within the year of follow-up, the cause of death was verified by examining the hospital medical records.

Statistical Analyses

For descriptive analysis, proportions were used for categorical variables and means with standard deviations were used for continuous variables. Demographic and clinical variables among different TOAST subtypes were compared by χ² test for categorical and analysis of variance test for continuous variables. The associations between HTN and stroke recurrence were analyzed in multivariable logistic regression models, after adjusting for potential confounders, including age, sex, history of stroke, diabetes mellitus, atrial fibrillation, dyslipidemia, coronary heart disease, smoking, drinking, stroke severity, and medication persistence during follow-up. Subanalyses of the data by TOAST subtypes were prespecified. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported separately. Two-tailed probability values are reported, and a probability value <0.05 was considered significant in univariable and multivariable analyses. Data were analyzed using SAS version 9.1.3 statistical software (SAS Institute, Inc., Cary, NC).

Results

Characteristics of Patient Population

Of the 22,216 patients enrolled in the China National Stroke Registry, 18,580 patients had complete baseline information and agreed to participate in follow-up. Among them, 12,415 had an IS. Among these IS patients, 855 patients were lost to follow-up during the first year, leaving 11,560 patients for the final analysis. Among this group entered into the final analysis, 8,409 (72.7%) had HTN (Figure 1). The clinical characteristics of the analyzed population (n=11,560), including the prevalence of HTN (P=0.09) and the distribution of TOAST subtypes (P=0.06), were generally similar to those of 855 patients who were lost to follow-up. However, patients who

Table 1. Baseline Characteristics Among Patients With Different Ischemic Stroke Subtypes

<table>
<thead>
<tr>
<th>Variables</th>
<th>LAA</th>
<th>SAO</th>
<th>CE</th>
<th>Other</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1915 (36.6%)</td>
<td>689 (55.6%)</td>
<td>414 (58.0%)</td>
<td>1424 (38.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>65.6±11.8</td>
<td>65.1±11.7</td>
<td>69.9±12.8</td>
<td>64.7±13.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4028 (76.9%)</td>
<td>1477 (76.2%)</td>
<td>462 (64.7%)</td>
<td>2442 (66.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1638 (31.3%)</td>
<td>584 (30.1%)</td>
<td>143 (20.0%)</td>
<td>884 (24.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>308 (5.9%)</td>
<td>68 (3.5%)</td>
<td>586 (82.1%)</td>
<td>292 (8.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3226 (61.6%)</td>
<td>1114 (57.5%)</td>
<td>312 (43.7%)</td>
<td>1596 (43.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of stroke</td>
<td>1860 (35.5%)</td>
<td>641 (33.1%)</td>
<td>235 (32.9%)</td>
<td>1231 (33.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>769 (14.7%)</td>
<td>246 (12.7%)</td>
<td>224 (31.4%)</td>
<td>495 (13.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current or previous smoker</td>
<td>2197 (41.6%)</td>
<td>776 (40.0%)</td>
<td>273 (38.2%)</td>
<td>1451 (39.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate or heavy drinking</td>
<td>549 (10.5%)</td>
<td>179 (9.2%)</td>
<td>67 (9.4%)</td>
<td>319 (8.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS scores at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>2445 (46.7%)</td>
<td>1295 (66.8%)</td>
<td>169 (23.7%)</td>
<td>1825 (49.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5–14</td>
<td>2196 (41.9%)</td>
<td>593 (30.6%)</td>
<td>270 (37.8%)</td>
<td>1325 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td>596 (11.4%)</td>
<td>50 (2.6%)</td>
<td>275 (38.5%)</td>
<td>521 (14.2%)</td>
<td></td>
</tr>
<tr>
<td>Persistence with antithrombotic drugs during follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High persistence (≥75%)†</td>
<td>2320 (44.3%)</td>
<td>769 (39.7%)</td>
<td>206 (28.8%)</td>
<td>1281 (34.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low persistence (&lt;75%)†</td>
<td>2367 (45.2%)</td>
<td>933 (48.1%)</td>
<td>324 (45.4%)</td>
<td>1843 (50.2%)</td>
<td></td>
</tr>
<tr>
<td>Nontreated†</td>
<td>550 (10.5%)</td>
<td>236 (12.2%)</td>
<td>184 (25.8%)</td>
<td>547 (14.9%)</td>
<td></td>
</tr>
<tr>
<td>Persistence with antihypertensive drugs during follow-up‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High persistence (≥75%)‡</td>
<td>1321 (32.8%)</td>
<td>496 (33.6%)</td>
<td>110 (23.8%)</td>
<td>732 (30.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low persistence (&lt;75%)‡</td>
<td>2111 (52.4%)</td>
<td>743 (50.3%)</td>
<td>187 (40.5%)</td>
<td>1106 (45.3%)</td>
<td></td>
</tr>
<tr>
<td>Untreated‡</td>
<td>596 (14.8%)</td>
<td>238 (16.1%)</td>
<td>165 (35.7%)</td>
<td>604 (24.7%)</td>
<td></td>
</tr>
</tbody>
</table>

CE indicates cardioembolism; LAA, large-artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; and SAO, small-artery occlusion.

*The P values are related to comparison between 4 groups.
†Persistence was calculated as the cumulative duration of taking medication divided by the length of the follow-up period. Persistence of ≥75% was defined as high and <75% was defined as low. Patients who did not take any medication during follow-up period were defined as untreated.
‡This analysis was limited in hypertensive patients.
were lost follow-up seemed less likely to have had a history of atrial fibrillation \((P=0.027)\) or severe stroke (National Institutes of Health Stroke Scale score \(\geq 15\) at admission; \(P<0.0001\)), compared with the study population (online-only Data Supplement Table I).

All 11,560 patients with IS (mean age 65.5 years [SD, 12.3]; 4,442 [38.4%] women), had brain CT or MRI and EKG. However, 2,578 patients (22.3%) had a Holter monitor, 2,230 (20.1%) had echocardiography (transthoracic or transesophageal), 5,257 patients (45.5%) had neurosonographic evaluations (carotid ultrasonography or transcranial Doppler), and 3,564 patients (30.8%) had angiographic evaluations (CT angiography, magnetic resonance angiography, or digital subtraction angiography). The overall interrater agreement for the TOAST classification was good, with a \(k\) value of 0.73 (95% CI, 0.65–0.81). Each of the IS patients was classified into a subtype: 5,237 (45.3%) with LAA, 1,938 (16.8%) with SAO, 714 (6.2%) with CE, and 3,671 (31.8%) with “Other” (Figure 1).

Baseline characteristics according to stroke subtypes are presented in Table 1. LAA and SAO subtype groups had a similar rate of HTN and diabetes mellitus, whereas SAO subtype had a milder stroke symptom on presentation. Patients with CE subtype were older and had a higher proportion of women, atrial fibrillation, coronary heart disease, and higher stroke severity scores on admission. This group was also less persistent with the antithrombotic or antihypertensive medications.

**Association Between HTN and Stroke Recurrence in Patients Stratified by IS Subtypes**

Table 2 shows the comparison of stroke recurrence rates at different time points between patients with or without HTN in each IS subtype. For the entire study population \((n=11,560)\), the cumulative stroke recurrence rate was 17.7% \((n=2,050)\) at 1 year after stroke onset. There was no statistically significant difference in stroke recurrence rates in patients with or without HTN at either 3 months (13.0% versus 12.9%; \(P=0.89\)), 6 months (16.2% versus 15.6%; \(P=0.48\)), or 1 year (18.0% versus 17.0%; \(P=0.21\)) after stroke onset. However, once they were stratified according to the IS subtypes, the stroke recurrence rate in the SAO subgroup was significantly greater in patients with HTN than in those without HTN (9.8% versus 6.3%, \(P=0.023\) at 3 months; 12.3% versus 8.7%, \(P=0.031\) at 6 months; 14.0% versus 9.3%, \(P=0.010\) at 1 year). In contrast, there were no statistically significant differences between patients with and without HTN in the LAA, CE, or “Other” subgroups. The stroke recurrence rates and probability values were listed in Table 2.

Furthermore, we used multivariable logistic regression analyses to investigate the association between HTN and risk of stroke recurrence. After adjusting for potential confounders, HTN was associated with stroke recurrence in the SAO subtype group at 3 months (OR, 1.77; 95% CI, 1.10–2.86), 6 months (OR, 1.48; 95% CI, 1.06–2.37), or 1 year (OR, 1.52; 95% CI, 1.03–2.31) after stroke onset. This phenomenon was not seen in the LAA, CE, or “Other” subgroups. The unadjusted and adjusted ORs with 95% CIs are shown in Figure 2.

**Other Risk Factors for Recurrent Stroke in Each IS Subtype**

Multivariable logistic analysis showed that diabetes mellitus, atrial fibrillation, and history of stroke were independent risk factors for recurrent stroke at 1 year in all IS subtypes, whereas dyslipidemia, smoking, and drinking had no association. Such as HTN, the impact of coronary heart disease on stroke recurrence varied according to IS subtypes (Table 3). The detailed ORs with 95% CIs of above risk factors are shown in Table II in the online-only Data Supplement.

**Discussion**

To the best of our knowledge, this is the largest observational study exploring HTN as a risk factor for stroke recurrence in patients with different IS subtypes. We identified HTN as a risk factor for stroke recurrence within 1 year in Chinese patients with the SAO subtype of IS, but not in other subtype groups.

The results of previous studies concerning the association between HTN and stroke recurrence have been inconsistent. A positive association between HTN and stroke recurrence was seen in the Stroke Data Bank study, the Lehigh Valley study, the Northern Manhattan stroke study, and the Nanjing Stroke Registry Program. In contrast, no association was found in the Oxfordshire Community Stroke Project study or the Rochester population study. These studies evaluated the association of HTN and recurrent stroke in all IS patients, regardless of the subtypes. It is clear now that racial-ethnic differences would have different proportions of IS subtypes, as reported in different stroke registries. As both the underlying pathogenesis...
and the role of HTN would vary among different IS subtypes, the results from these previous studies were nonconclusive.

In this study, the positive association between HTN and stroke recurrence was only found in SAO subtype. This is consistent with the results of 2 previous clinical trials, which showed that lacunar strokes have a greater response to blood pressure-lowering strategy than other IS subtypes. As we know, lacunar infarction is usually caused by occlusion of a single, small, deep penetrating artery or one of its branches. HTN is characterized by lipohyalinosis and fibrinoid necrosis, particularly taking place in penetrating arteries.17 HTN-related strokes are mainly lacunar infarctions or intracerebral hemorrhage because of rupture of resistance vessels affected by those pathological processes.18 Russell was the first to propose that treatment of HTN may prevent hemorrhagic and lacunar strokes, but not those because of atherosclerosis.17 Observations in a community blood pressure control study supported the hypothesis, and showed that the strokes prevented by treating HTN are mostly because of hypertensive small-vessel diseases. To our knowledge, the PROGRESS study was the only trial that examined the various subtypes of the outcomes of stroke in a secondary prevention setting, although the initial strokes were not subclassified. It showed that the risk of lacunar stroke was reduced almost by one quarter with active antihypertensive treatment. However, to date, no studies have answered the question directly, whether the HTN contributes to stroke recurrence in different subtypes of initial IS. In this large observational study, our results imply that, among patients with initial IS, the association of HTN with stroke recurrence is related to the IS subtype. HTN plays an important role for stroke recurrence within 1 year in patients with the SAO subtype, but not in LAA, CE, or “Other” subtype groups. Besides HTN, in this study, we also investigated the impact of other traditional risk factors on stroke recurrence in each IS subtype. The factors that are most constantly associated with recurrence among different subtypes are diabetes mellitus, atrial fibrillation, and history of stroke. It is worth noting that

| Table 3. Risk Factors for Recurrent Stroke in Each IS Subtype |
|--------------------|---|---|---|---|
| Risk Factors        | LAA | SAO | CE | Other |
| Hypertension        | −   | +   | −  | −    |
| Diabetes mellitus   | −   | +   | +  | +    |
| Atrial fibrillation | +   | +   | +  | +    |
| Dyslipidemia        | −   | −   | −  | −    |
| History of stroke   | +   | +   | +  | +    |
| Coronary heart disease | +   | –   | –  | –    |
| Current or previous smoking | −   | –   | –  | –    |
| Moderate or heavy drinking | −   | −   | –  | –    |

CE indicates cardioembolism; LAA, large-artery atherosclerosis; and SAO, small-artery occlusion.
coronary heart disease was associated with stroke recurrence in LAA other than SAO, CE, or “Other” subtypes. This may be attributed to the same pathogenesis between myocardial infarction and LAA.

Our study also demonstrated differences among subtypes for recurrence rate, at 3 months, 6 months, or 1 year (Table 2). The recurrence rate was highest for CE stroke, followed by LAA stroke, and lowest for SAO stroke. Our result was different from Western population studies,20–22 in which a high recurrence risk was confirmed for IS LAA, and a minimum risk for lacunar stroke. The highest recurrence rate for patients with CE subtype in our study may be attributable to the older age, higher proportion of risk factors, and lower persistence with secondary prevention medication after discharge, compared with those with the other stroke subtypes.

Our study had some limitations. First, our data came from a hospital-based registry, which could have hospital selection bias,21 including a greater number of patients with LAA or CE stroke, who would experience more severe symptoms than patients with an SAO stroke. Second, patients who were lost to follow-up had milder stroke than study population, which could also lead to selection bias. Third, blood pressure during the follow-up period was not recorded in the registry, and we could not evaluate the effect of blood pressure control and its impact on stroke recurrence. However, we used the level of persistence with antihypertensive medication during follow-up to reflect the control of blood pressure.24 Finally, although we classified the subtypes of initial IS using the TOAST criteria, we could not classify the subtypes of recurrent stroke, as this information was not collected in the registry. It is likely that after the initial lacunar stroke, a recurrence is more likely to be another lacunar stroke.25

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Disclosures

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. Yilong Wang was responsible for study design, data analyses, and drafting/revising the manuscript; Jie Xu was responsible for acquisition of data, data analyses, and drafting the manuscript; Xingquan Zhao, David Wang, Chunxue Wang, and Liping Liu were involved in revising the manuscript for important intellectual content; Hao Li, Anxin Wang, and Xia Meng conducted the statistical analysis; and Yongjun Wang was responsible for the study concept or design, technical, material support, administration, and supervision.

References

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Supplemental Methods

Assessment of medication compliance

In this study, the compliance levels of antihypertensive and antithrombotic agents were calculated separately but used the same criteria. Compliance was defined as the overall duration of medication therapy. Compliance with antihypertensive therapy was assessed through the telephone interview. At the 3-, 6-, and 12-month intervals after initial stroke, patients were asked whether they had taken antihypertensive therapy since their last follow up. A ‘yes’ answer at the 3- month follow-up was defined as 3 months’ duration of therapy. A ‘yes’ answer at 6-month follow-up indicated that a patient had been taking medicine from 3-month to 6 month. A ‘yes’ answer at 12-month follow-up indicated that a patient had been taking medicine from 6-month to 12 month.

Compliance was calculated as the ratio of the cumulative duration of antihypertensive therapy and the duration of overall follow-up before the recurrence event. For example, if a patient had a recurrent stroke at 12-month follow up, a ‘yes’ answer with antihypertensive drugs used at 3-month follow up, a “no” answer at 6-month and a “yes” answer at 12-month, the compliance level was calculated as (3+0+6)/12=75%. If a patient had a recurrent stroke at 6-month follow up, a ‘yes’ answer with antihypertensive drugs used at 3-month follow up, but had a “no” answer at 6-month, the compliance level was calculated as (3+0)/6=50%. If a patient had a recurrent stroke at 3-month follow up, and a ‘yes’ answer with antihypertensive drugs used at 3-month follow up, the compliance level was calculated as 3/3=100%. Compliance of $\geq 75\%$ was defined as high and $< 75\%$ was defined as low. Patients who did
not take any medication during follow-up period were defined as untreated.

**Supplemental Tables**

**Supplemental Table e-1.** Baseline characteristics of patients with acute ischemic stroke who did or did not have 1-year follow-up data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Follow-up Data (n = 11,560)</th>
<th>Patients Lost to Follow-up (n = 855)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4,442 (38.4%)</td>
<td>315 (36.8%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–45</td>
<td>721 (6.2%)</td>
<td>61 (7.1%)</td>
<td>0.68</td>
</tr>
<tr>
<td>46–65</td>
<td>4,662 (40.3%)</td>
<td>351 (41.1%)</td>
<td></td>
</tr>
<tr>
<td>66–75</td>
<td>3,567 (30.9%)</td>
<td>256 (29.9%)</td>
<td></td>
</tr>
<tr>
<td>≥76</td>
<td>2,610 (22.6%)</td>
<td>187 (21.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td>3,967 (34.3%)</td>
<td>267 (31.2%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8409 (72.7%)</td>
<td>599 (70.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1,685 (14.6%)</td>
<td>107 (12.5%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1,254 (10.9%)</td>
<td>72 (8.4%)</td>
<td>0.032</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3,249 (28.1%)</td>
<td>237 (27.7%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>6,248 (54.1%)</td>
<td>478 (55.9%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3,166 (27.4%)</td>
<td>242 (28.3%)</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Variable | Patients with Follow-up Data (n = 11,560) | Patients Lost to Follow-up (n = 855) | P value
---|---|---|---
Moderate or heavy drinking | 1,082 (9.4%) | 89 (10.4%) | 0.31

**Other clinical features**

**NIHSS scores at admission**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 0-4 | 5,734 (49.5%) | 490 (57.3%) | <0.0001
| 5-14 | 4,384 (38.0%) | 291 (34.0%) |
| ≥15 | 1,442 (12.5%) | 74 (8.7%) |

**Ischemic stroke subtype**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| LAA | 5237 (45.3%) | 350 (40.9%) | 0.06
| SAO | 1938 (16.8%) | 152 (17.8%) |
| CE | 714 (6.2%) | 49 (5.7%) |
| others | 3671 (31.8%) | 304 (35.6%) |

Data shown are n (%).

Abbreviations: CE, cardioembolism; LAA, large-artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SAO, small-artery occlusion.

**Supplemental Table e-2.** Risk factors for recurrent stroke in each ischemic stroke subtype.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>LAA (95% CI)</th>
<th>SAO (95% CI)</th>
<th>CE (95% CI)</th>
<th>Other (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.99 (0.81-1.21)</td>
<td>1.52 (1.03-2.31)</td>
<td>1.14 (0.75-1.73)</td>
<td>0.88 (0.71-1.09)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.18 (1.01-1.38)</td>
<td>1.14 (1.08-1.93)</td>
<td>1.21 (1.06-2.36)</td>
<td>1.25 (1.02-1.53)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.77 (1.36-2.31)</td>
<td>2.14 (1.18-3.88)</td>
<td>1.25 (1.09-2.28)</td>
<td>1.80 (1.36-2.38)</td>
</tr>
<tr>
<td>Condition</td>
<td>Odds Ratio 1</td>
<td>95% CI</td>
<td>Odds Ratio 2</td>
<td>95% CI</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.92 (0.75-1.13)</td>
<td>0.76 (0.49-1.17)</td>
<td>0.89 (0.55-1.42)</td>
<td>0.91 (0.71-1.16)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>1.59 (1.37-1.85)</td>
<td>1.86 (1.41-2.47)</td>
<td>1.58 (1.11-2.26)</td>
<td>1.55 (1.29-1.86)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.35 (1.11-1.65)</td>
<td>1.24 (0.84-1.83)</td>
<td>1.07 (0.74-1.56)</td>
<td>1.03 (0.80-1.33)</td>
</tr>
<tr>
<td>Current smokers*</td>
<td>0.91 (0.73-1.12)</td>
<td>1.01 (0.69-1.48)</td>
<td>1.61 (0.91-2.85)</td>
<td>0.95 (0.74-1.24)</td>
</tr>
<tr>
<td>Moderate or heavy drinking</td>
<td>1.04 (0.79-1.36)</td>
<td>0.84 (0.49-1.44)</td>
<td>0.48 (0.17-1.31)</td>
<td>0.99 (0.69-1.41)</td>
</tr>
</tbody>
</table>

*Odds ratios for “current smokers” vs “never smoked”. Abbreviations: CE, cardioembolism; LAA, large-artery atherosclerosis; SAO, small-artery occlusion.

**Supplemental References**