

Subtyping of Ischemic Stroke Based on Vascular Imaging: Analysis of 1,167 Acute, Consecutive Patients

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Background and Purpose: Knowledge of a patient's cerebral vascular status is essential for accurately classifying stroke. However, vascular evaluations have been incomplete in previous studies, and a stroke registry based on the results of such vascular investigations has not been reported. The purpose of the present study was to classify ischemic strokes based on vascular imaging data.

Methods: Between May 2001 and August 2003, 1,264 patients with acute (< 7 days) ischemic stroke were admitted to Asan Medical Center. Among them, 1,167 patients (750 men and 417 women; mean age 63.3 years) underwent an angiogram (mostly a magnetic resonance angiogram) and were included in this study. Electrocardiography and computed tomography/magnetic resonance imaging were performed in all patients, while 31.2% underwent echocardiography. The subtypes were categorized with the aid of a modification of the Trial of ORG 10172 in the Acute Stroke Treatment classification.

Results: Large-artery atherosclerosis (LAA) was the most frequent subtype (42%), followed by small-vessel occlusion (SVO, 27%), cardiogenic embolism (CE, 15%), undetermined etiology (15%), and other determined etiology (1.5%). Risk factors included hypertension (71%), cigarette smoking (35%), diabetes mellitus (30%), history of previous stroke (22.7%), emboligenic cardiac diseases (20%), and hypercholesterolemia (11%). Hypertension was more common in patients with SVO than in those with other subtypes ($p<0.05$), and the case-fatality rate was higher in patients with CE than in those with other subtypes ($p<0.01$). The functional outcome was worse in patients with LAA than in those with other stroke subtypes ($p<0.01$).

Conclusion: According to the stroke registry based on vascular imaging results, LAA was the most common stroke subtype followed by SVD. The high incidence of LAA is probably related to the increased identification of the presence of intracranial atherosclerosis by MR angiogram.

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Key Words : Cerebrovascular disease, Angiogram, Registry, Diagnosis

INTRODUCTION

It is important to have an appropriate classification system for ischemic stroke because the clinical course,

treatment modality, and prognosis may differ between the different stroke subtypes. Of the many available classification schemes, the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) criteria has been the most widely used, and is based on a patient's neuro-

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logical signs, brain imaging findings, and ancillary diagnostic tests.¹ However, there is no methodological obligation for a vessel investigation such as magnetic resonance angiogram (MRA) or conventional angiogram in the TOAST classification, and most reported stroke registries utilize only Doppler ultrasound data. The information obtained from carotid Doppler scanning is limited to the extracranial carotid artery. Although intracranial diseases can be assessed with transcranial Doppler ultrasound, the data are also limited because this method is not sufficiently sensitive to evaluate mild stenosis or distal artery diseases. Moreover, the data obtained vary with the operator and cannot be obtained in a significant portion of older women. This has led to the increasing use of magnetic resonance imaging (MRI) and MRA, which allow the status of the vessels (especially the intracranial vessels) to be examined noninvasively. The purpose of this study was to determine the frequency of occurrence of each stroke subtype using modified TOAST criteria based on MRI and vascular investigations results in a large tertiary hospital. We therefore retrospectively analyzed stroke registries from 1,167 consecutive patients who underwent vascular investigations.

SUBJECTS AND METHODS

Between May 2001 and August 2003, 1,678 stroke patients were admitted to the Neurology Department of Asan Medical Center (AMC) and registered on the AMC Stroke Registry. Patients with subarachnoid hemorrhage, arteriovenous malformation, or traumatic hemorrhages were not considered for this registry. The data in the AMC Stroke Registry included demographics, present stroke/transient ischemic attack (TIA) history (e.g., onset time, symptoms at onset, and change of symptoms from onset), risk factors (e.g., hypertension, diabetes, cardiac disease, cigarette smoking, alcohol drinking, and past history of stroke), family history of stroke, initial neurologic examination, and diagnostic evaluation and treatment. Investigations included (1) neuroimaging (computed tomography [CT] or MRI), (2) vessel investigation (MRA, conventional angiography, or

CT angiogram), (3) 12-lead electrocardiography (ECG), and (4) standard blood and urine tests. Echocardiography (transthoracic and/or esophageal approaches) were performed in selected patients (1) who had any history or clinical or ECG evidence of cardiac abnormalities, and were thus ordered by a physician to undergo in-depth cardiac evaluation, (2) in whom infective endocarditis was suspected, (3) who were young (age <50 years) without risk factors for atherosclerosis, or (4) with unclear mechanisms (i.e., small cortical infarction with normal ECG and normal vascular imaging results, even if the patient was older than 50 years).

Neuroimaging and clinical studies revealed that 1,325 patients had ischemic stroke (75.3%), 98 patients had TIA (5.8%), and 255 patients had hemorrhagic stroke (13.4%). Among them, 1,264 patients visited the medical center within 7 days after the onset of stroke, and 1,167 patients underwent vessel investigation (mostly MRA, conventional angiogram in 18, CT angiogram in 10) within 7 days (2.26 ± 1.38 days, mean \pm SD). These 1,167 patients were included in this study. Of the excluded 97 patients (8.3%), the reasons for not undergoing vessel investigation were the reluctance of the patient or a relative thereof to undergo the study, due mainly to economic reasons ($n=39$), poor or uncooperative conditions ($n=31$), delayed performance of the vessel investigation ($n=13$), early transferral to other hospitals ($n=6$), the presence of a pacemaker ($n=3$), and other miscellaneous reasons ($n=5$). Transthoracic/transesophageal echocardiography was performed in 362 patients (31%). Among them, 15 patients could not undergo a transesophageal procedure due to a lack of cooperation or the reluctance of the patient.

These 1,167 patients were classified based on a modification of the TOAST classification and angiogram results. We considered significant (>50%) narrowing or occlusion as clinically significant arterial disease in the extracranial arteries. However, because mild intracranial disease may produce stroke by way of perforating artery occlusion,² mild (<50%) stenosis was also considered as clinically significant in patients with intracranial artery diseases if (1) the patient's infarction was considered to be caused by the intracranial disease by at least two of the three stroke neurologists, or (2) a radiologist who

Table 1. Subtypes of ischemic stroke

| Stroke subtype | Total (n=1,167) | Men (n=750) | Women (n=417) |
|------------------------------|-----------------|-------------|---------------|
| Large-artery atherosclerosis | 491 (42.1) | 315 (42.0) | 176 (42.2) |
| Cardiogenic embolism | 177 (15.2) | 112 (14.9) | 65 (15.6) |
| Small-vessel occlusion | 313 (26.8) | 204 (27.2) | 109 (26.1) |
| Undetermined etiology | 169 (14.5) | 108 (14.4) | 61 (14.6) |
| Two or more causes | 66 (5.7) | 38 (5.1) | 28 (6.7) |
| Not fit in any category | 89 (7.6) | 61 (8.1) | 28 (6.7) |
| Incomplete investigation | 14 (1.2) | 9 (1.2) | 5 (1.2) |
| Other determined etiology | 17 (1.5) | 11 (1.4) | 6 (1.4) |

Data are presented as *n*(%) values

Table 2. Clinical characteristics of patients with different subtypes of ischemic stroke

| | Total (n=1167) | LAA (n=491) | CE (n=177) | SVO (n=313) | UD (n=169) | OD (n=17) |
|-----------------------|-------------------|----------------|---------------|----------------|---------------|--------------|
| Mean age (years) | 63.3 | 64.2 | 64.6 | 62.4 | 52.8 | 61.9 |
| Hypertension | 829 (71.0) | 344 (70.1) | 113 (63.8) | 239 (76.4) | 122 (72.2) | 11 (64.7) |
| Cigarette smoking | 408 (35.0) | 174 (35.4) | 51 (28.8) | 123 (39.3) | 57 (33.7) | 3 (17.6) |
| Diabetes mellitus | 346 (29.6) | 170 (34.6) | 32 (18.1) | 95 (30.4) | 47 (27.8) | 2 (11.8) |
| Previous stroke | 253 (21.7) | 115 (23.4) | 35 (19.8) | 48 (15.3) | 54 (32.0) | 1 (5.9) |
| Cardiac disease | 229 (19.6) | 0 (0) | 173 (97.7) | 0 (0) | 54 (32.0) | 2 (11.8) |
| High risk | 112 (9.6) | 0 | 93 (52.5) | 0 | 17 (10.1) | 2 (11.8) |
| Medium risk | 117 (10.0) | 0 | 80 (45.2) | 0 | 37 (21.9) | 0 |
| Hyperlipidemia | 130 (11.1) | 62 (12.6) | 16 (9.0) | 37 (11.8) | 13 (7.7) | 2 (11.8) |
| Modified Rankin scale | | | | | | |
| Independent (0-2) | 782 (67.0) | 287 (58.5) | 117 (66.1) | 264 (84.3) | 104 (61.5) | 10 (58.8) |
| Dependent (3-5) | 363 (31.1) | 199 (40.5) | 54 (30.5) | 49 (15.7) | 54 (32.0) | 7 (41.2) |
| Death (6) | 22 (1.9) | 5 (1.0) | 6 (3.4) | 0 (0) | 11 (6.5) | 0 (0) |

Data are presented as *n*(%) values. LAA; large-artery atherosclerosis, CE; cardiogenic embolism, SVO; small-vessel occlusion, UD; undetermined etiology, OD; other determined etiology

was blind to the clinical findings considered the vascular stenosis to be real.

Thus, the stroke subtypes were categorized as follows:

1. Large-artery atherosclerosis (LAA): Patients with significant stenosis or occlusion of intracranial or extracranial arteries that is considered to be responsible for the stroke. Patients should not have sources of cardiogenic embolism (CE).

2. CE: Patients with an embolism with a cardiac source without evidence of significant large-vessel disease.

3. Small-vessel occlusion (SVO): Small (< 2 cm in diameter), deep lesions visible on CT/MRI without potential sources of CE and significant large-artery diseases.

4. Other determined etiology (OD): Patients have rare causes of stroke such as, for example, moyamoya

disease, vasculitis, venous thrombosis, or dissection.

5. Undetermined etiology (UD): Patients with (a) incomplete evaluation, (b) two or more possible mechanisms, and (c) an etiology that does not fit into any of the above categories. The outcome of the patients was assessed with the aid of a modified Rankin scale at the time of discharge.

Statistical analysis was performed using SPSS for Windows. The Pearson chi-square test was applied to examine the difference in categorical risk factors between the subtypes of ischemic stroke. Differences were considered significant when $p < 0.05$.

RESULTS

Of the 1,167 patients, there were 750 men and 417

Table 3. Relative incidences of each stroke subtypes by Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) or modified TOAST reported from selected stroke registries

| Study | Authors and publication year | LAA | CE | SVO | OD | UD |
|------------------------------|-------------------------------|------|------|------|-----|------|
| TOAST | Madden et al. 1995 | 31 | 20 | 31 | 2 | 15 |
| Athens Stroke Registry | Vemmos et al. 2000 | 18 | 37 | 20 | 4 | 21 |
| SCAN-IV | Yip et al. 1997 | 17 | 20 | 29 | 6 | 29 |
| Barcelona Stroke Registry | Marti-Vilalta and Arboix 1999 | 39.5 | 17.5 | 11 | 3.3 | 17.5 |
| Yonsei Stroke Registry | Lee et al. 2001 | 16.5 | 18.5 | 21.5 | 3.1 | 40.6 |
| Hallym Registry | Lee et al. 2005 | 42.0 | 8.7 | 31 | 1.9 | 16.4 |
| Asan Medical Center Registry | Kim et al. 2006 | 42.9 | 14.9 | 26.3 | 1.5 | 14.4 |

Data are percentages

women (age 63.3 ± 11.8 years, range 15-94 years). Table 1 lists the ischemic stroke subtypes and their relative frequencies. LAA was the most frequent stroke subtype (42.1%), followed by SVO (26.8%), CE (15.2%), UD (14.5%), and OD (1.5%). The distributions of the subtypes did not differ significantly between men and women.

Among the 491 patients with LAA, tandem lesions were seen in 21 patients (4.3%) in whom the responsible vascular lesion was not identifiable. In others, the LAA lesion responsible for the ischemic stroke was found most frequently in the middle cerebral artery (37.7%), followed by the internal carotid artery (28.3%), vertebral artery (14.6%), posterior cerebral artery (8.8%), basilar artery (7.8%), and anterior cerebral artery (2.0%).

Hypertension was the most important risk factor, being found in 71% of patients, followed by cigarette smoking (35%), diabetes mellitus (29.6%), a history of previous stroke (21.7%), emboligenic cardiac disease (19.6%), and hyperlipidemia (11.1%) 4.6% of the patients had no known risk factors. The risk factors did not differ between men and women.

Table 2 lists the risk factors associated with the various stroke subtypes. Multiple logistic regression analysis revealed that hypertension was more common in patients with SVO than in those with other subtypes ($p < 0.05$). The in-hospital case-fatality rate was 1.9%. The highest case-fatality rate was highest in patients with the UD subtype (6.5%). Excluding UD, the case-fatality rate was higher in patients with CE (3.4%) than in those with other subtypes ($p < 0.01$). A modified

Rankin scale score of 0-2 at discharge was classified as independent, and a score of 3-5 as dependent. The functional outcome was worse in patients with OD (41.2%) and LAA (40.5%) than in those with other subtypes ($p < 0.01$).

DISCUSSION

We found that LAA was the most frequent (43%) stroke subtype in our registry. Among the recent hospital-based registries (Table 3), an incidence of around 40% was found only in the Barcelona Stroke Registry³ and Hallym Registry,⁴ while others found lower incidences of LAA.⁵⁻⁸

There are three possible explanations for the relatively high frequency of LAA observed in this study. First, it may be attributable to the relatively complete work-up carried out in our series. It is noteworthy that the portion of patients with UD was much lower in our registry than in others, especially those from Asian countries.^{6,8} We performed a vascular imaging investigation in all of the patients, whereas this was performed in only a limited number of patients in previous registries. Therefore, it is possible that the significant portion of UD in other series could have been categorized as LAA caused by intracranial atherosclerosis if the vascular status had been adequately evaluated. This assumption is also based on Asians more often having intracranial artery diseases than extracranial artery diseases.^{2,9,10} Indeed, in our registry, the middle cerebral artery was the most

common location of atherosclerosis related to ischemic stroke.

Second, the definition of LAA applied to our classification system differed from the original TOAST classification, which might have contributed to the higher frequency of LAA because strokes associated with mild intracranial atherosclerosis (<50%) were classified as LAA when judged as being relevant.

Finally, CE occurred infrequently in this study, which may have increased the relative frequency of LAA. Admittedly, these results might be attributable to inadequate cardiac work-ups. Although we performed ECG on all the patients, an echocardiogram was obtained in only 31.2% of the patients. Thus, a more vigorous cardiac examination would have resulted in an increased incidence of CE. However, the chances of detecting a cardiac embolic source were very low in our series, even with an echocardiogram.¹¹ Moreover, the significance of echocardiologic findings such as a patent foramen ovale, mitral valve prolapse, or aorta atheroma as potential sources of the embolism has been recently questioned.¹²⁻¹⁴ Thus, a recent consensus does not recommend using echocardiogram in patients with established stroke mechanisms.¹⁵

Our results might therefore reflect the actual low incidence of CE. Other registries in Korea have also shown a relatively low incidence of CE.^{4,8} One possible explanation for this observation would be that our stroke patients were younger (mean age 63 years) than patients in Western studies. Because atrial fibrillation - the most frequent cardioembolic source¹⁶ - is closely associated with increasing age,^{17,18} CE may be a less important cause of stroke in a relatively young population. Indeed, as indicated in Table 3, the Athens Stroke Registry had a high proportion of CE, while the Barcelona Stroke Registry showed a relatively small proportion of CE. The mean age in the Athens registry was 70.2 years, while that in the Barcelona registry was 66 years. Another explanation could be that myocardial infarction is less common among Koreans than among Caucasians.

Hypertension was the most important risk factor, being found in 71.0% of patients, followed by cigarette smoking (35.0%) and diabetes mellitus (29.6%). Hypertension was a more powerful risk factor for

patients with SVO (76.4%) than for those with other stroke subtypes. This result was consistent with those of other registries.^{3,4,7,8}

We found that the in-hospital case-fatality rate was very low (1.9%). A low hospital mortality rate was also observed in other recent registries.^{4,8} The low fatality rate could be related to the increased detection of mild stroke with the use of MRI or improved management of strokes, perhaps with the use of thrombolysis. However, this interpretation should be made with caution because we included only those patients who underwent vascular imaging. Therefore, certain patients who could not undergo vascular work-up due to unstable vital signs or poor general condition were excluded.

In this study the case-fatality rate was highest in patients with the UD subtype (6.5%). Because UD was defined when the patients had two or more stroke mechanisms or when the work-up was incomplete, patients with multiple cardiovascular problems or those with an unstable clinical condition might be more common in this group than in others. If UD was excluded, patients with the CE subtype had the highest case-fatality rate, while patients with SVO had the lowest fatality rate. This result is consistent with previous results.⁶⁻⁸ The Framingham study also showed that stroke severity in patients with atrial fibrillation was greater than those without.¹⁹ However, in our registry the functional outcome, as assessed using the modified Rankin scale, was worst for patients with LAA.

This study is subject to several limitations. First, because the results are based on a registry from a large tertiary hospital, selection bias is inevitable. Admitted patients may have had more severe symptoms than those visiting smaller hospitals. On the other hand, patients with extremely severe symptoms might have died at home or might have been discharged at the emergency room without admission. To minimize this problem, we included only those patients with acute stroke (i.e., those admitted < 7 days after the onset). In addition, it is likely that patients with poor clinical condition or those with financial difficulties did not undergo vascular investigations. Because these patients were excluded, our subjects were also biased in this sense. However, to see the possible subtype difference between the included and

excluded patients, we classified stroke subtypes in the excluded 97 patients using a criterion used in a previous study.³ We found that LAA ($n=30$, 30.9%) was still the most frequent subtype, followed by SVO ($n=24$, 24.7%) and CE ($n=20$, 20.6%). Thus, the proportion of each stroke subtype was not greatly influenced by the exclusion of these patients.

REFERENCES

1. Adams HJ Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41.
2. Kim JS, Kang DW, Kwon SU. Intracranial atherosclerosis: incidence, diagnosis and treatment. *J Clin Neurol* 2005;1:1-7.
3. Marti-Vilalta JL, Arboix A. The Barcelona Stroke Registry. *Eur Neurol* 1999;41:135-142.
4. Lee BC, Hwang SH, Jung S, Yu KH, Lee JH, Cho SJ, et al. The Hallym Stroke Registry: a web-based stroke data bank with an analysis of 1,654 consecutive patients with acute stroke. *Eur Neurol* 2005;54:81-87.
5. Madden KP, Karanjia PN, Adams HP Jr, Clarke WR. Accuracy of initial stroke subtype diagnosis in the TOAST study. Trial of ORG 10172 in Acute Stroke Treatment. *Neurology* 1995;45:1975-1979.
6. Yip PK, Jeng JS, Lee TK, Chang YC, Huang ZS, Ng SK, et al. Subtypes of ischemic stroke. A hospital-based stroke registry in Taiwan (SCAN-IV). *Stroke* 1997;28:2507-2512.
7. Vemmos KN, Takis CE, Georgilis K, Zakopoulos NA, Lekakis JP, Papamichael CM, et al. The Athens stroke registry: results of a five-year hospital-based study. *Cerebrovasc Dis* 2000;10:133-141.
8. Lee BI, Nam HS, Heo JH, Kim DI, Yonsei Stroke Team. Yonsei Stroke Registry. Analysis of 1,000 patients with acute cerebral infarctions. *Cerebrovasc Dis* 2001;12:145-151.
9. Nishimaru K, McHenry LC Jr, Toole JF. Cerebral angiographic and clinical differences in carotid system transient ischemic attacks between American Caucasian and Japanese patients. *Stroke* 1984;15:56-59.
10. Liu HM, Tu YK, Yip PK, Su CT. Evaluation of intracranial and extracranial carotid steno-occlusive diseases in Taiwan Chinese patients with MR angiography: preliminary experience. *Stroke* 1996;27:650-653.
11. Cho AH, Kang DW, Kwon SU, Kim JS. Is 1.5 cm Size Criterion for Lacunar Infarction Still Valid? A Study on Strictly Subcortical Middle Cerebral Artery Territory Infarction Using Diffusion-Weighted MRI. *Cerebrovasc Dis* 2006;23:14-19.
12. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005;58:688-697.
13. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Christianson TJ, et al. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc* 2006;81:602-608.
14. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Sicks JD, et al. Population-based study of the relationship between atherosclerotic aortic debris and cerebrovascular ischemic events. *Mayo Clin Proc* 2006;81:609-614.
15. Kapral MK, Silver FL. Preventive health care, 1999 update: 2. Echocardiography for the detection of a cardiac source of embolus in patients with stroke. Canadian Task Force on Preventive Health Care. *CMAJ* 1999;161:989-996.
16. Becker E, Jung A, Voller H, Wegscheider K, Landgraf H. Cardiogenic embolism - The main cause of stroke in a city hospital. *Cerebrovasc Dis* 1996;6:97.
17. Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. *Stroke* 1985;16:182-188.
18. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation: The Copenhagen Stroke Study. *Stroke* 1996;27:1765-1769.
19. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996;27:1760-1764.