Original Investigation

Cerebral Microbleeds and Early Recurrent Stroke After Transient Ischemic Attack

Results from the Korean Transient Ischemic Attack Expression Registry

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IMPORTANCE The risk of early recurrent stroke after transient ischemic attack (TIA) may be modifiable by optimal treatment. Although ABCD^2 scores, diffusion-weighted imaging lesions, and large artery stenosis are well known to predict early stroke recurrence, other neuroimaging parameters, such as cerebral microbleeds (CMBs), have not been well explored in patients with TIA.

OBJECTIVE To determine the rate of early recurrent stroke after TIA and its neuroimaging predictors.

DESIGN, SETTING, AND PARTICIPANTS In this hospital-based, multicenter prospective cohort study, consecutive patients with TIA were enrolled from 11 university hospitals from July 1, 2010, through December 31, 2012. Patients who were admitted within 24 hours after symptom onset and underwent diffusion-weighted imaging were included.

MAIN OUTCOMES AND MEASURES The primary end point was recurrent stroke within 90 days. Baseline demographics, clinical manifestations, neuroimaging findings, and use of antithrombotics or statins also were analyzed.

RESULTS A total of 500 patients (mean age, 64 years; male, 291 [58.2%]; median ABCD^2 score, 4) completed 90-day follow-up with guideline-based management: antiplatelets (457 [91.4%]), anticoagulants (74 [14.8%]), and statins (345 [69.0%]). Recurrent stroke occurred in 25 patients (5.0%). Compared with patients without recurrent stroke, those with recurrent stroke were more likely to have crescendo TIA (20 [4.2%] vs 4 [16.0%], $P = .03$), white matter hyperintensities (146 [30.7%] vs 13 [52.0%], $P = .03$), and CMBs (36 [7.6%] vs 7 [28.0%], $P = .003$). On multivariable Cox proportional hazards analysis, CMBs remained as independent predictors for recurrent stroke (hazard ratio, 3.66; 95% CI, 1.47-9.09; $P = .005$).

CONCLUSIONS AND RELEVANCE Immediate and optimal management seems to modify the risk of recurrent stroke after TIA. Cerebral microbleeds may be novel predictors of stroke recurrence, which needs further validation.

JAMA Neurol. doi:10.1001/jamaneurol.2014.3958
Published online January 12, 2015.

Supplemental content at jamaneurology.com

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Patients with transient ischemic attack (TIA) are at high risk of early recurrent stroke. However, the rate of early recurrent stroke is variable (0.6%-20.6%) across studies,[1,2] depending on study design, target population, completeness of follow-up, and management. Studies[3,4] published in the middle 2000s and later tend to reveal lower rates of recurrent stroke compared with those published between the late 1990s and early 2000s. In particular, urgent evaluation and immediate treatment could substantially modify the risk, preventing approximately 80% of early recurrent strokes.[3]

The ABCD^2 score, a simple and widely used risk estimation scheme based on clinical variables, was developed to identify high-risk patients in primary care or emergency department settings.[5] The ABCD^2 score is based on 5 parameters (age, blood pressure, clinical features, duration of TIA, and presence of diabetes). However, this score does not include additional prognostic information obtained from more detailed investigations. For a better risk prediction, several strategies have been developed to further include potential prognostic variables of recurrent TIA, atrial fibrillation, acute ischemic lesion on diffusion-weighted imaging (DWI), and symptomatic carotid stenosis.[6-10] However, imaging markers of small vessel disease, such as white matter hyperintensities (WMHs) or cerebral microbleeds (CMBs), which are prevalent in the elderly population and known as predictors of recurrent stroke, have not been well investigated in patients with TIA.[11,12] Using a prospective registry, we aimed to investigate the rate of 90-day recurrent stroke and the prognostic significance of WMHs or CMBs and other well-recognized risk predictors.

Methods

Study Design and Participants

This study was approved by the institutional review boards of all participating hospitals, and written informed consent was obtained from all patients or their legally authorized representatives.

We designed a hospital-based, multicenter prospective cohort study. Consecutive patients with TIA were enrolled from 11 university hospitals from July 1, 2010, through December 31, 2012. We defined TIA as focal neurologic deficits lasting less than 24 hours.[13] Patients 40 years or older who were admitted within 24 hours of symptom onset and who underwent magnetic resonance imaging (MRI), including DWI and magnetic resonance angiography, were included in the study. Patients with focal neurologic deficits caused by migraine, seizures, syncope, peripheral vertigo, and transient global amnesia were excluded. We strongly recommended that participating physicians adhere to the current treatment guidelines.[14]

Study Variables

Using the Korean Transient Ischemic Attack Expression Registry, we prospectively compiled data on patient demographics, laboratory results, characteristics of the index TIA, MRIs, and treatments. The characteristics of the index TIA included recent prior TIA, presenting symptoms and signs, and duration of symptoms. Duration of symptoms was categorized into less than 10 minutes, 10 through 59 minutes, and 60 minutes or longer.[14] Crescendo TIA was defined as at least 3 similar attacks within 7 days from the index TIA.[15] ABCD^2, ABCD^3, and ABCD^3-I scores were also determined.[5,7] In addition, we investigated the presumptive Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classifications of index TIA events in patients with DWI lesions.[16]

We assessed acute lesions on DWI (single or multiple) and chronic lesions on T2-weighted or fluid-attenuated inversion recovery imaging and gradient-recalled echo (GRE) imaging, including prior territorial infarction, lacunar infarction, intracerebral hemorrhages, WMHs, and CMBs. The WMHs were graded according to the modified visual grading system of Fazekas et al[17] and dichotomized into negative (scores, 0-1) and positive (scores, 2-3) groups.[18] The CMBs were defined as focal, round, low-signal-intensity lesions with a diameter less than 10 mm on GRE imaging[19] (**Figure 1**). The number of CMBs was counted on GRE imaging.[20] The degree of stenosis was measured using previously known methods,[21,22] and more than 50% narrowing was considered significant. The MRI findings were analyzed by an independent radiologist of the central core imaging laboratory who was masked to the 90-day stroke recurrence. Detailed parameters for MRI acquisitions are described in eTable 1 in the Supplement.

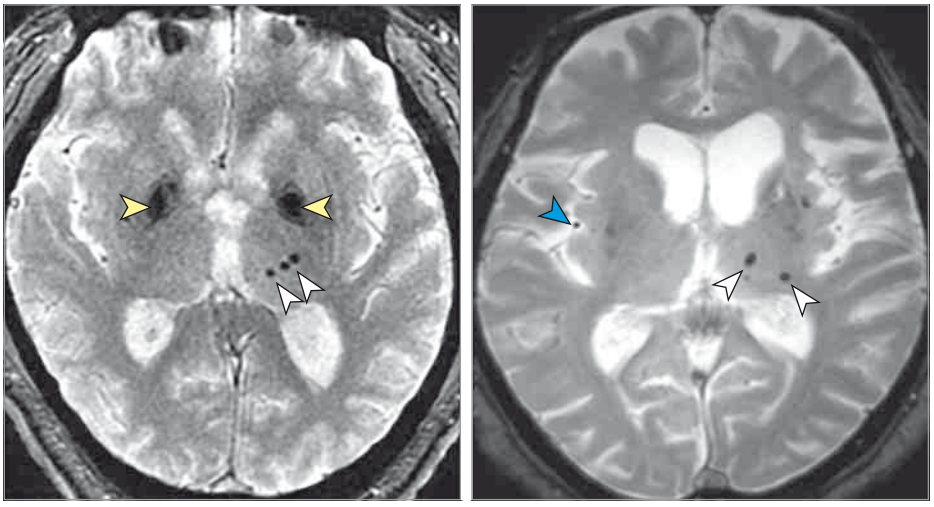
Primary End Point

The primary end point was recurrent stroke within 90 days, which was determined via outpatient clinic or by telephone interview with a structured questionnaire. If necessary, we reviewed medical records to confirm the diagnosis of recurrent stroke.

Statistical Analysis

For univariable analysis, we used the *t* tests for continuous variables and the Pearson χ^2 tests and Fisher exact tests for categorical variables. For ordinal variables, the extended Mantel-Haenszel χ^2 test for testing a linear trend was used. In multivariable analyses, prognostic variables of demographics, blood pressure, diabetes mellitus, and TIA characteristics were combined into the ABCD^2 score to avoid overfitting because the number of recurrent stroke was small. In addition to variables with $P < .05$ in the univariable analyses, multivariable models included variables of acute DWI lesion and symptomatic intracranial or extracranial stenosis of 50% or greater. To further assess the independent association of small vessel disease markers with 90-day recurrent stroke, we used additional multivariable models that adjusted for ABCD^3 and ABCD^3-I scores. We incorporated these composite scores instead of using each individual variable, such as DWI lesions and symptomatic stenosis, to decrease the number of covariates. The ABCD^2, ABCD^3, and ABCD^3-I scores are recognized not to fulfill a linearity assumption.[7] Therefore, for analytical purposes, we categorized the scores based on observations in a previous study[7] and our data as follows: ABCD^2 scores into scores of 0 through 3, 4 and 5, and 6 and 7; ABCD^3 scores into scores of 0 through 3, 4 and 5, and 6 through 9; and ABCD^3-I scores into scores of 0 through 3, 4 through 7, and 8 through 13.

Figure 1. T2-Weighted Gradient Echo Imaging Revealing Cerebral Microbleeds (CMBs)



Both images show multiple CMBs in the thalamic regions (white arrowheads). The CMBs are distinguished from calcifications (yellow arrowheads) and cerebral vessels (blue arrowhead).

Hazard ratios (HRs) of recurrent stroke and their 95% CIs were estimated with adjustments for possible confounders using Cox proportional hazards models. Statistical analyses were performed with SPSS statistical software version 21 (SPSS Inc) and R version 3.0.1 (R Core Team), and a 2-sided $P < .05$ was considered the minimum level of statistical significance.

Results

Patients

Of the 521 consecutive patients with TIA screened during the study period, 500 (96.0%) were enrolled; 21 patients were excluded because of protocol violation or consent withdrawal. The demographic characteristics and cardiovascular risk factors did not differ between the included and excluded patients (eTable 2 in the Supplement).

The mean age was 64 years, and 291 (58.2%) were male. The median ABCD^2 score was 4, and the distribution was 29.0% (ABCD^2 score, 0-3), 52.4% (ABCD^2 score, 4-5), and 18.6% (ABCD^2 score, 6-7). Motor weakness was the most common presenting symptom (313 [62.6%]), followed by speech disturbance (101 [20.2%]). Symptoms lasted for 60 minutes or longer in 222 patients (44.4%), 10 through 59 minutes in 168 (33.6%), and less than 10 minutes in 110 (22.0%). Prior TIA within 7 days was present in 77 patients (15.4%), and 24 (4.8%) had a crescendo TIA.

All patients underwent MRI, which was completed within 48 hours after symptom onset in 499 patients (99.8%). Acute DWI lesions were present in 150 patients (30.0%), WMHs in 159 (31.8%), and CMBs in 43 (8.6%). Eighteen patients had a single CMB, 18 had 2 to 4 CMBs, and 7 had 5 or more CMBs. Symptomatic intraocclusion or extracranial steno-occlusion was found in 183 patients (36.6%). After the index TIA, 457 patients (91.4%) were treated with antiplatelet therapy, 74 (14.8%) with anticoagulation, and 345 (69.0%) with statins. Thirty-six patients (7.2%) were prescribed both antiplatelets and anticoagulants because of coexisting coronary artery disease or other causes combined with atrial fibrillation. The rate of antithrombotic prescription did not differ between the patients with and without CMBs (38 [88.4%] of 43 vs 419 [91.7%] of 457, $P = .40$, for antiplatelets; 6 [14.0%] of 43 vs 68 [14.9%] of 457, $P = .87$, for 9 anticoagulants). Among 40 patients with symptomatic extracranial stenosis, 17 patients have undergone carotid intervention (14 with carotid stenting and 3 with endarterectomy). Detailed baseline data for all patients and their comparisons between patients with a subsequent stroke within 90 days and those without are summarized in **Table 1** and eTable 3 in the Supplement.

Considering that the exact determination of the TOAST classifications of index TIA might be difficult, the classification was limited to the 150 patients with acute ischemic lesions in DWI. Large artery atherosclerosis was the most common subtype (65 [43.3%]) followed by undetermined (28 [18.7%]), cardioembolism (27 [18.0%]), small vessel occlusion (24 [16.0%]), and other conditions (≥2 subtypes, 6 [4.0%]).

Recurrent Stroke Within 90 Days and Risk Factors

Recurrent ischemic stroke occurred in 25 patients (5.0%) among 500 patients within 90 days, and 14 (56.0%) occurred within 7 days. When categorized by the ABCD^2 score, the rate of stroke at 90 days was 2.8% (ABCD^2 score, 0-3), 5.9% (ABCD^2 score, 4-5), and 6.5% (ABCD^2 score, 6-7) (P for trend = .17). As for the TOAST classifications of recurrent strokes, small vessel occlusion consisted of nearly half the patients (12 [48.0%] of 25) followed by large artery atherosclerosis (11 [44.0%] of 25), cardioembolism (1 [4.0%] of 25), and other conditions (1 [4.0%] of 25, cancer related).

eTable 3 and eTable 4 in the Supplement summarize the results of unadjusted analyses for the association of the baseline clinical and imaging characteristics with the 90-day stroke occurrence. Patients with ABCD^2 scores of 4 or higher had a higher stroke rate than those with ABCD^2 scores less than 4, but the difference was not statistically significant (21 [5.9%] of 355 vs 4 [2.8%] of 145, $P = .14$). Most clinical variables were not significantly associated with a subsequent stroke. However, patients with crescendo TIA had a substantially higher

Table 1. Baseline Characteristics of the Study Population[a]

Characteristic	Total (N = 500)	Recurrent Stroke After TIA		*P* Value
		Absent (n = 475)	Present (n = 25)	
Age, mean (SD), y	64.4 (11.8)	64.3 (11.8)	68.0 (12.8)	.12
Male sex	291 (58.2)	275 (57.9)	16 (64.0)	.55
Cardiovascular risk factors				
Hypertension	333 (66.6)	313 (65.9)	20 (80.0)	.15
Diabetes mellitus	149 (29.8)	141 (29.7)	8 (32.0)	.81
Hyperlipidemia	157 (31.4)	149 (31.4)	8 (32.0)	.95
Atrial fibrillation	53 (10.6)	52 (10.9)	1 (4.0)	.50[b]
Coronary artery disease	42 (8.4)	41 (8.6)	1 (4.0)	.71[b]
Smoking	131 (26.2)	126 (26.5)	5 (20.0)	.47
History of stroke	87 (17.4)	82 (17.3)	5 (20.0)	.79[b]
Family history of stroke	104 (20.8)	98 (20.6)	6 (24.0)	.69
Anthropometric measures, mean (SD)				
Abdominal circumference, cm	86.9 (9.3)	86.9 (9.2)	86.9 (11.5)	.99
Systolic blood pressure, mm Hg	147.9 (27.8)	147.5 (27.6)	157.2 (30.1)	.09
Diastolic blood pressure, mm Hg	83.1 (16.1)	83.0 (16.2)	83.8 (15.0)	.83
Outcome acquisition methods				
Outpatient clinic	369 (73.8)	351 (73.9)	18 (72.0)	.83
Telephone follow-up	131 (26.2)	124 (26.1)	7 (28.0)	
Presenting symptoms and signs				
Motor weakness	313 (62.6)	293 (61.7)	20 (80.0)	.07
Speech disturbance	101 (20.2)	97 (20.4)	4 (16.0)	.59
Symptom duration, min				
<10	110 (22.0)	104 (21.9)	6 (24.0)	.08
10-59	168 (33.6)	155 (32.6)	13 (52.0)	
≥60	222 (44.4)	216 (45.5)	6 (24.0)	
Prior TIA before the index TIA				
<24 h	106 (21.2)	94 (19.8)	12 (48.0)	.001
<7 d	77 (15.4)	70 (14.7)	7 (28.0)	.08[b]
Crescendo TIA	24 (4.8)	20 (4.2)	4 (16.0)	.03[b]
$ABCD^2$ score	4.27 (1.41)	4.25 (1.41)	4.68 (1.35)	.14
Low risk (scores, 0-3)	145 (29.0)	141 (29.7)	4 (16.0)	.13[c]
Medium risk (scores, 4-5)	262 (52.4)	247 (52.0)	15 (60.0)	
High risk (scores, 6-7)	93 (18.6)	87 (18.3)	6 (24.0)	
Corresponding vascular territory				
Carotid	242 (48.4)	228 (48.0)	14 (56.0)	.70[b]
Vertebrobasilar	78 (15.6)	74 (15.6)	4 (16.0)	
Undetermined	180 (36.0)	173 (36.4)	7 (28.0)	
DWI lesions	150 (30.0)	140 (29.5)	10 (40.0)	.26
Single	92 (18.4)	86 (18.1)	6 (24.0)	.44[b]
Multiple	58 (11.6)	54 (11.4)	4 (16.0)	.52
Symptomatic steno-occlusion	183 (36.6)	173 (36.4)	10 (40.0)	.72
Territorial infarction	44 (8.8)	43 (9.1)	1 (4.0)	.71[b]
Lacunar infarct	89 (17.8)	81 (17.1)	8 (32.0)	.06[b]
ICH	10 (2.0)	9 (1.9)	1 (4.0)	.40[b]
WMHs	159 (31.8)	146 (30.7)	13 (52.0)	.03
CMBs	43 (8.6)	36 (7.6)	7 (28.0)	.003[b]
Carotid intervention				
No	483 (96.6)	458 (96.4)	25 (100)	.82[b]
Yes	17 (3.4)	17 (3.6)	0	

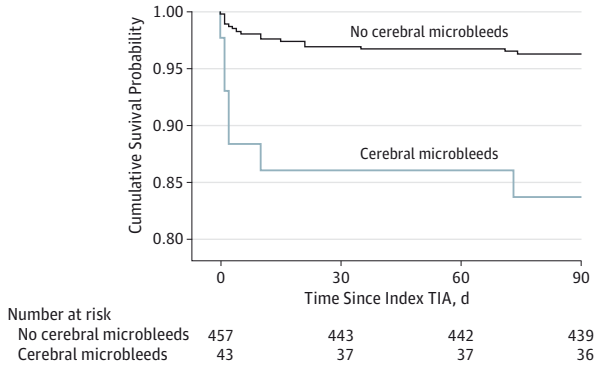
Abbreviations: CMBs, cerebral microbleeds; DWI, diffusion-weighted imaging; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; TIA, transient ischemic attack; WMHs, white matter hyperintensities.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Fisher exact test.

[c] Extended Mantel-Haenszel χ^2 test for linear trend.

Figure 2. Kaplan-Meier Curves of Recurrent Stroke Rate According to the Presence of Cerebral Microbleeds



TIA indicates transient ischemic attack.

stroke rate than those without (4 [16.7%] of 24 vs 21 [4.4%] of 476; HR, 3.96; 95% CI, 1.36-11.54; $P = .01$). In addition, prior TIA within 24 hours was associated with a higher 90-day stroke rate (HR, 1.28; 95% CI, 1.03-1.60; $P = .03$).

Among MRI variables, WMHs and CMBs were significantly associated with a higher risk of subsequent stroke. Thirteen (8.2%) of 159 patients with WMHs had a stroke within 90 days compared with 12 (3.5%) of 341 without WMHs (HR, 2.40; 95% CI, 1.10-5.26; $P = .03$). Of 43 patients with CMBs, 7 (16.3%) had a subsequent stroke, which was substantially higher than 18 (3.9%) of 457 without CMBs (HR, 4.47; 95% CI, 1.87-10.70; $P < .01$) (**Figure 2**). In contrast, the recurrent stroke rate was higher in patients with acute DWI lesions than those without, but the difference was not statistically significant (10 [6.7%] of 150 vs 15 [4.3%] of 350; HR, 1.57; 95% CI, 0.71-3.50; $P = .27$). In addition, symptomatic stenosis was not associated with an increased risk of subsequent stroke (HR, 1.15; 95% CI, 0.52-2.55; $P = .74$).

From univariable analyses, the multivariable model that incorporated the ABCD^2 score additionally included variables of crescendo TIA, DWI lesions, symptomatic stenosis, WMHs, and CMBs. We included only crescendo TIA rather than prior TIA within 24 hours before the index TIA to avoid the risk of overfitting and multicollinearity based on the observation of their crude HRs. In this multivariable Cox proportional hazards model, CMBs were the significant independent factor for the 90-day subsequent stroke (adjusted HR, 3.69; 95% CI, 1.42-9.60; $P < .01$) (**Table 2**).

Because of concerns about overfitting, we reduced the number of covariates in the additional multivariable models using the composite scores ABCD^3 and ABCD^3-I instead of the ABCD^2 scores. The ABCD^3-I scores were dichotomized because there was no recurrent stroke in the subgroup of ABCD^3-I scores 0 through 3. The CMBs still remained significant in these multivariable models (Table 2).

Carotid intervention did not affect the results of the multiple Cox proportional hazards model (adjusted HR for CMB, 3.63; 95% CI, 1.46-9.00; $P < .01$ in model 3, including carotid intervention). In addition, patients with multiple CMBs had 6.5 times the risk than those without CMB (adjusted HR, 6.5; 95% CI, 2.6-16.7; $P < .01$ in model 3).

Table 2. Multivariable Cox Proportional Hazards Models for Magnetic Resonance Imaging Predictors of Recurrent Stroke

Model	Hazard Ratio (95% CI)	*P* Value
Model 1		
ABCD^2 score 4-5[a]	1.89 (0.61-5.79)	.27
ABCD^2 score 6-7[a]	2.03 (0.56-7.36)	.28
Crescendo TIA	2.53 (0.84-7.68)	.10
DWI lesion	1.74 (0.75-4.06)	.20
Symptomatic stenosis	0.97 (0.43-2.19)	.94
WMHs	1.70 (0.74-3.89)	.21
CMBs	3.69 (1.42-9.60)	.008
Model 2		
ABCD^3 score 4-5[a]	2.97 (0.67-13.10)	.15
ABCD^3 score 6-9[a]	3.12 (0.66-14.72)	.15
DWI lesion	1.89 (0.83-4.32)	.13
Symptomatic stenosis	0.95 (0.42-2.13)	.89
WMHs	1.77 (0.77-4.07)	.18
CMBs	3.92 (1.55-9.96)	.004
Model 3		
ABCD^3-I score 8-13[b]	1.52 (0.65-3.57)	.34
WMHs	1.78 (0.78-4.09)	.17
CMBs	3.66 (1.47-9.09)	.005

Abbreviation: CMBs, cerebral microbleeds; DWI, diffusion-weighted imaging; TIA, transient ischemic attack; WMHs, white matter hyperintensities.

[a] Compared with lowest category (scores, 0-3).

[b] Compared with ABCD^3-I (scores, 0-7) because there was no recurrent stroke in the ABCD3-I subgroup of scores 0 through 3.

Discussion

This hospital-based, multicenter prospective cohort study found a 5.0% recurrence stroke rate within 90 days after TIA. In the setting of urgent evaluation and management, the CMBs were independent predictors of subsequent ischemic stroke after adjusting for other prognostic variables.

The 90-day stroke rate of 5.0% in our study was lower than the mean rate of previous studies (8.5%, **Table 3**). The proportions of patients with ABCD^2 scores of 4 or higher was 71.0%, and DWI lesions were present in 30.0%, findings comparable with those of previous studies. The lower rate of 90-day recurrent stroke observed in this study might be attributed to immediate and optimal management. All participating hospitals were comprehensive stroke centers, and all patients were admitted and underwent immediate diagnostic workup. In addition, optimal management was given according to the current practice guidelines, reflected by the high prescription rates of antiplatelets (94.9%), anticoagulants (14.8%), and statins (69.0%). Our result is in line with previous studies[3,4] that found a low recurrent stroke rate with these treatment strategies.

It is noteworthy that CMBs were substantially and independently associated with an increased risk of recurrent stroke

Table 3. Characteristics of Major Studies of Transient Ischemic Attack With Recurrent Rates at 90-Days

Source	Study Site	Design	No. of Patients at Enrollment/ No. of Patients at 90 Days[a]	Recurrence Rate at 90 Days, %	Mean Age, y	Patients, %				
						Motor Deficit	DWI Lesion	Symptomatic Extracranial Steno-occlusion	Antiplatelets	Anticoagulation
Johnston et al,[23] 2000	Multiple EDs in the United States	Retrospective	1707	10.5	72.0	46.0	NA	NA	80	14
Gladstone et al,[24] 2004	Multiple EDs in Canada	Prospective	265	6.4	71.0	65.0	NA	NA	63	7
Hill et al,[25] 2004	Multiple EDs in Canada	Retrospective	2285	9.5	71.4	NA	NA	NA	NA	NA
Lisabeth et al,[26] 2004	Population-based study in the United States	Prospective	362	5.8	72.3	67.0	NA	NA	67	15
Kleindorfer et al,[27] 2005	Multiple EDs in the United States	Retrospective	1023	14.6	70.4	NA	NA	NA	NA	NA
Correia et al,[28] 2006	Population-based study in Portugal	Prospective	141	20.6	69.9	NA	NA	NA	NA	NA
Cucchiara et al,[29] 2006	Specialist service in the United States	Prospective	117/116	1.7	63.0	36.0	25.0	14.0	71	30
Johnston et al,[5] 2007	Multiple EDs in the United States	Retrospective	1069	10	NA	44.0	NA	NA	81	9
Johnston et al,[5] 2007	Clinics in the United States	Retrospective	962	6	NA	33.0	NA	NA	82	7
Bray et al,[30] 2007	Single ED in Australia	Retrospective	102/98	7.1	73.0	33.0	NA	NA	82	7
Calvet et al,[31] 2007	Specialist service in France	Prospective	203/201	3.5	61.2	54.0	32.0		72	28
Rothwell et al,[3] 2007	Specialist service in the United Kingdom	Prospective	160	0.6	71.4	35.0	NA	NA	90	8
Lavallée et al,[4] 2007	Specialist service in France	Prospective	629	1.9	66.0	39.0	NA	NA	90	9
Merwick et al,[7] 2010	Hospital-based study in North America and Europe	Retrospective	2654/1877	3.9	65.4	NA	34.7	11.8	NA	NA
Song et al,[32] 2013	Hospital-based study in China	Prospective	248/239	12.1	57.4	67.4	33.1	15.9	NA	NA
Present study	Specialist service in Korea	Prospective	500/500	5.0	64.4	65.0	30.0	10.8	94.9	14.8

Abbreviations: ED, emergency department; DWI, diffusion-weighted imaging; NA, not applicable.

[a] Number of patients at 90 days was not available for all the studies.

after TIA in our study. A meta-analysis[11] with patients with ischemic stroke and TIA found that CMBs increased the risk of recurrent ischemic stroke and intracerebral hemorrhage. However, the meta-analysis[11] was not able to adjust for the confounding variables, and the results were largely derived from patients with ischemic stroke rather than TIA. In a European study[33] exclusively including patients with TIA, CMBs conferred a 9-fold increased risk of recurrent ischemic stroke. Our study also found robust findings of the independent association of CMBs with recurrent ischemic stroke across several multivariable models that adjusted for covariates. In addition, the greater risk with multiple CMBs than with a single CMB would further support this association.

Cerebral microbleeds are widely recognized as risk factors for hemorrhagic stroke, but the pathophysiologic link between CMBs and ischemic stroke remains unclear. The prevailing underlying pathologic change around CMBs is lipohyalinosis.[11,34] It was hypothesized that CMBs might harm small vessels, which results in in-situ thrombosis and reduced arterial flow distal to CMBs.[33,35] In addition, CMBs are likely to reflect vessel fragility and endothelial instability, which would increase the risk of ischemic stroke and hemorrhagic stroke.[36] A previous study[11] found that CMBs shared risk factors for future ischemic stroke with other small vessel diseases. Thus, the mechanisms of ischemic stroke recurrence might be explained in the same context with patients with lacunar infarctions or WMHs. Significant predictors of recurrent lacunar infarctions are hypertension and diabetes.[37] It is generally recognized that the risk of early recurrent stroke after TIA is higher with large artery atherosclerosis or

cardioembolism[38]; however, the risk could be substantially modified by statins, antiplatelets, and anticoagulants.[39] In contrast, these therapies might not effectively block the mechanisms of recurrent stroke related to CMB-related conditions, which might be associated with longstanding hypertension or cerebral amyloid angiopathy. As a result, we assume that CMBs remained as significant predictors of recurrent stroke in this study.

Physicians' avoidance of prescribing antithrombotics because of concern of hemorrhagic stroke in patients with CMBs may be an issue. However, the rate of antithrombotic prescription did not differ between the patients with and without CMBs in our study.

In our results, the most frequent TOAST classification of recurrent stroke was small vessel occlusion (12 [48.0%] of 25). Although this is contradictory to most previous data indicating a relatively low risk of early stroke recurrence with lacunar stroke,[40] there are also conflicting reports. In a previous study,[39] the risk of recurrent stroke based on TOAST classification was 11% in large artery disease, 11% in cardioembolic, 20% in small vessel occlusion, 3% in cryptogenic, and 5% in other conditions. This result might reflect the prognostic changes by recently developed treatment strategies, although it needs to be validated by additional research.

Our study has limitations. This study had a small number of patients with subsequent strokes and accordingly was not adequately powered to detect the associations of other predictors with the 90-day stroke. We explored the statistical significance through various multivariable models with composite scores to reduce the risk of an overfitting problem.[7] Although CMBs were still strong and robust independent predictors despite the small number of outcome events, there are possibilities that our study might be underpowered to detect the effects of various factors.

Furthermore, the study participants were limited to an Asian population. The relative proportions of small vessel occlusion in stroke mechanism was higher in Asian countries compared with those of Western countries.[41] In addition, all patients were recruited and hospitalized in comprehensive stroke centers, which restricts the generalizability of our findings.

Nevertheless, our study has notable strengths in that 500 patients with acute TIA were enrolled within 24 hours, 99.8% underwent MRI and magnetic resonance angiography evaluation within 48 hours of symptom onset, and 100% completed 90-day follow-up with adequate secondary prevention management. Therefore, the current findings might be relevant to well-organized stroke care settings and add up-to-date information on outcome and neuroimaging predictors in patients with TIA.

Conclusions

Immediate and optimal management seems to modify the risk of early recurrent stroke after TIA. Cerebral microbleeds may be a novel predictor of stroke recurrence after TIA, which remains to be validated by additional studies.

ARTICLE INFORMATION

Accepted for Publication: October 29, 2014.

Published Online: January 12, 2015. doi:10.1001/jamaneurol.2014.3958.

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Obtained funding: Y.-S. Lee.
Administrative, technical, or material support: Kim, Bae, Kwon, S.-H. Lee, Rha, Koo, Yu, Seo, K. B. Lee, Y.-S. Lee.
Study supervision: Hong, Kim, Bang, Bae, Park, Rha, Y.-S. Lee.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grants RES10-RF136, 800-20100046, and 800-20100055 from the Seoul National University Research and Development Business Foundation.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Contribution: Soo Chin Kim, MD, Department of Radiology, Seoul National University Boramae Medical Center, analyzed the neuroimaging data. Dr Kim did not receive financial compensation.

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