Burden of Intracranial Atherosclerosis Is Associated With Long-Term Vascular Outcome in Patients With Ischemic Stroke

Byung-Su Kim, MD, PhD; Pil-Wook Chung, MD, PhD; Kwang-Yeol Park, MD, PhD; Hong-Hee Won, PhD; Oh Young Bang, MD, PhD; Chin-Sang Chung, MD, PhD; Kwang Ho Lee, MD, PhD; Gyeong-Moon Kim, MD, PhD

Background and Purpose—Ischemic stroke patients often have intracranial atherosclerosis (ICAS), despite heterogeneity in the cause of stroke. We tested the hypothesis that ICAS burden can independently reflect the risk of long-term vascular outcome.

Methods—This was a retrospective cohort study analyzing data from a prospective stroke registry enrolling consecutive patients with acute ischemic stroke or transient ischemic attack. A total of 1081 patients were categorized into no ICAS, single ICAS, and advanced ICAS (ICAS ≥2 different intracranial arteries) groups. Primary and secondary end points were time to occurrence of recurrent ischemic stroke and composite vascular outcome, respectively. Study end points by ICAS burden were compared using Cox proportional hazards models in overall and propensity-matched patients.

Results—ICAS was present in 405 patients (37.3%). During a median 5-year follow-up, recurrent stroke and composite vascular outcome occurred in 6.8% and 16.8% of patients, respectively. As the number of ICAS increased, the risk for study end points increased after adjustment of potential covariates (hazard ratio per 1 increase in ICAS, 1.19; 95% confidence interval, 1.01–1.42 for recurrent ischemic stroke and hazard ratio, 1.18; 95% confidence interval, 1.05–1.33 for composite vascular outcome). The hazard ratios (95% confidence interval) for recurrent stroke and composite vascular outcome in patients with advanced ICAS compared with those without ICAS were 1.56 (0.88–2.74) and 1.72 (1.17–2.53), respectively, in the overall patients. The corresponding values in the propensity-matched patients were 1.28 (0.71–2.30) and 1.95 (1.27–2.99), respectively.

Conclusions—ICAS burden was independently associated with the risk of subsequent composite vascular outcome in patients with ischemic stroke. These findings suggest that ICAS burden can reflect the risk of long-term vascular outcome. **(*Stroke*. 2017;48:2819-2826. DOI: 10.1161/STROKEAHA.117.017806.)**

Key Words: intracranial atherosclerosis ■ propensity score ■ recurrence ■ registries ■ risk factors ■ stroke

Intracranial atherosclerosis (ICAS) refers to atherosclerotic lesions involving large intracranial cerebral arteries.[1–3] ICAS is a major cause of ischemic stroke worldwide and can occur in isolation or as part of systemic atherosclerosis.[1,4–6] Although ischemic stroke can be because of a wide array of causes, numerous studies have reported that patients with ischemic stroke often had ICAS regardless of clinical relevance.[6] This can be simply explained by the fact that ischemic stroke shares common risk factors with ICAS.[1–3] Moreover, although ICAS was once considered a characteristic of Asian, black, and Hispanic populations, recent investigations have indicated a substantial influence of ICAS in white populations.[4,6–8]

In this context, there have been few efforts to identify the predictive value of ICAS with respect to long-term vascular outcome in patients with ischemic stroke. Existing studies have reported that presence or extent of ICAS was associated with the risk of recurrent stroke and mortality.[9–11] Nevertheless, it remains undetermined whether the association is independent of index stroke pathogenesis, conventional vascular risk factors, cardioembolic source, and extracranial carotid atherosclerosis. Furthermore, the pathogenesis of recurrent stroke has rarely been reported with respect to ICAS burden.

Therefore, we tested the hypothesis that higher burden of ICAS, regardless of its clinical relevance, could be an independent biomarker reflecting long-term vascular risk using

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From the Department of Neurology, Bundang Jesaeng General Hospital, Seongnam, Korea (B.-S.K.); Department of Neurology, Samsung Medical Center (B.-S.K., O.Y.B., C.-S.C., K.H.L., G.-M.K) and Department of Neurology, Kangbuk Samsung Hospital (P.-W.C.), Sungkyunkwan University School of Medicine, Seoul, Korea; Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea (K.-Y.P.); and Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Samsung Medical Center, Seoul, Korea (H.-H.W.).

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Correspondence to Gyeong-Moon Kim, MD, PhD, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-Dong, Kangnam-Gu, Seoul 135–710, South Korea. E-mail kimgm@skku.edu

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data from a cohort of consecutive ischemic stroke patients. In addition, we investigated whether ICAS burden was associated with the large artery atherosclerosis (LAA) pathogenesis in patients experiencing recurrent ischemic stroke.

Methods

Study Design and Patients

This was a retrospective cohort study using stroke registry data from a single tertiary university hospital (Seoul, Korea) from April 2006 to May 2009. Consecutive patients with ischemic stroke or transient ischemic attack (TIA) who were admitted within 7 days of stroke symptom onset were prospectively enrolled in the registry. We comprehensively collected data on demographic and clinical information, vascular risk factors, medication at the onset of index stroke, and stroke syndrome. Based on comprehensive data and results of workups, stroke pathogenesis was determined according to the TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment).[12] Patients were excluded if they had missing data, did not participate in the first follow-up after discharge, were transferred to another hospital during admission, or died because of index stroke or other serious medical illness during admission. Each patient (or their guardian) gave written informed consent for participation in the study. The study was approved by the local institutional review board.

Measurement

Each patient underwent 3-Tesla magnetic resonance imaging (Achieva; Philips Medical System, Best, the Netherlands). Steno-occlusive lesions of intracranial and extracranial cerebral arteries were mainly measured using 3-dimensional time-of-flight magnetic resonance angiography and contrast-enhanced magnetic resonance angiography during the admission period. In some patients who did not undergo magnetic resonance angiography or with contraindication to magnetic resonance imaging, angiographic assessment was conducted based on computed tomographic angiography or cerebral angiography.

Significant atherosclerotic lesion was defined as ≥ 50% stenosis or occlusion of the large intracranial cerebral and extracranial carotid arteries.[13–15] Presence of significant ICAS was determined in the intracranial segments of the internal carotid and vertebral arteries and the basilar artery and the proximal segments of the middle cerebral artery, anterior cerebral artery, and posterior cerebral artery. Angiographic interpretation was based on the consensus of 2 experienced neuroradiologists who were blind to clinical data and results of workups. Next, to reduce the possibility of misclassification of nonatherosclerotic steno-occlusive lesions (eg, embolic occlusion, dissection-related stenosis, and cerebral vasculitis) as ICAS, we reaffirmed cerebral arterial steno-occlusive lesions of limited patients with confirmed cardioembolic source or other evident cause of steno-occlusive lesions.[15] ICAS burden was defined as a total number of the above intracranial arteries with significant stenosis, regardless

Table 1. Baseline Characteristics, Stratified by ICAS Burden in the Overall and Propensity-Matched Patients

	Overall Patients				Propensity-Matched Patients				Standardized Difference, Advanced vs Single ICAS	Standardized Difference, Advanced vs No ICAS
	No ICAS (n=676)	Single ICAS (n=220)	Advanced ICAS (n=185)	*P* Value	No ICAS (n=368)	Single ICAS (n=184)	Advanced ICAS (n=184)	*P* Value		
Age, y	62.6±12.7	65.2±12.3	66.5±12.6	<0.001	65.4±11.1	65.7±11.5	66.5±12.6	0.562	0.064	0.089
Male sex, n (%)	425 (62.9)	141 (64.1)	109 (58.9)	0.525	219 (59.5)	112 (60.9)	109 (59.2)	0.940	0.033	0.006
Body mass index, kg/m^2	24.0±3.1	24.1±3.1	23.6±3.1	0.370	23.8±3.0	23.8±3.0	23.6±3.1	0.759	−0.055	−0.063
Risk factors, n (%)										
Hypertension	403 (59.6)	153 (69.5)	144 (77.8)	<0.001	263 (71.5)	134 (72.8)	143 (77.7)	0.288	−0.117	−0.150
Diabetes mellitus	165 (24.4)	71 (32.3)	84 (45.4)	<0.001	122 (33.2)	70 (38.0)	83 (45.1)	0.023	−0.142	−0.240
Dyslipidemia	161 (23.8)	55 (25.0)	60 (32.4)	0.057	108 (29.3)	54 (29.3)	59 (32.1)	0.785	−0.058	−0.058
Current smoking	171 (25.3)	56 (25.5)	32 (17.3)	0.066	74 (20.1)	36 (19.6)	32 (17.4)	0.743	0.057	0.071
Coronary heart disease	51 (7.5)	22 (10.0)	16 (8.6)	0.266	32 (8.7)	18 (9.8)	16 (8.7)	0.905	0.039	0.000
Cardioembolic source	198 (29.2)	43 (19.5)	24 (13.5)	<0.001	77 (20.9)	27 (14.7)	25 (13.6)	0.051	0.032	0.214
Previous stroke/TIA	117 (17.3)	58 (26.4)	58 (31.4)	<0.001	78 (21.2)	53 (28.8)	58 (31.5)	0.017	−0.058	−0.222
ECCAS ≥50%, n (%)	94 (13.9)	40 (18.2)	41 (22.2)	0.017	71 (19.3)	37 (20.1)	41 (22.3)	0.772	−0.052	−0.072
Stroke pathogenesis, n (%)				<0.001				<0.001	−0.058	−0.385
LAA	80 (11.8)	116 (52.7)	113 (61.1)		78 (21.2)	99 (53.8)	113 (61.4)			
Cardioembolism	178 (26.3)	27 (12.3)	13 (7.0)		73 (19.8)	16 (8.7)	13 (7.1)			
Small vessel occlusion	204 (30.2)	40 (18.2)	20 (10.8)		162 (44.0)	35 (19.0)	20 (10.9)			
Other pathogenesis	61 (9.0)	14 (6.4)	13 (7.0)		18 (4.9)	13 (7.1)	12 (6.5)			
Undetermined	153 (22.6)	23 (10.5)	26 (14.1)		37 (10.1)	21 (11.4)	26 (14.1)			
Secondary prevention, n (%)										
Antiplatelets	516 (76.3)	186 (84.5)	152 (82.2)	0.017	295 (80.2)	154 (83.7)	152 (82.6)	0.630	0.028	−0.064
Anticoagulants	199 (29.4)	56 (25.5)	47 (25.4)	0.364	101 (27.4)	47 (25.5)	46 (25.0)	0.781	0.012	0.056
Statin	323 (47.8)	125 (56.8)	106 (57.3)	0.013	201 (54.6)	103 (56.0)	105 (57.1)	0.808	−0.022	−0.049

Data are presented as mean±SD or n (%). ECCAS indicates extracranial carotid atherosclerosis; ICAS, intracranial atherosclerosis; LAA, large artery atherosclerosis; and TIA, transient ischemic attack.

of clinical relevance. Based on the final angiographic assessment, patients were categorized into 3 groups: no ICAS, single ICAS, and advanced ICAS (significant ICAS ≥2 different large intracranial arteries). Each process during angiographic assessment and classification was completed by assessors who were blind to the clinical outcome of patients.

Follow-Up and Outcome Assessment

During follow-up, treatment for secondary stroke prevention (management of vascular risk factors, lifestyle modification, and antithrombotic therapy) followed standard stroke care protocols of our hospital. All patients (and guardians if relevant) regularly visited the outpatient clinic at 1- to 6-month intervals and were followed up to February 28, 2015.

The primary study outcome was the time to occurrence of recurrent ischemic stroke. Clinical worsening because of systemic or metabolic cause, neurological deterioration related to cerebral edema, or hemorrhagic transformation of index stroke was not regarded as a recurrent event. The secondary outcome was the time to occurrence of composite vascular outcome, including recurrent ischemic stroke, TIA, hemorrhagic stroke, acute coronary syndrome, and vascular death.[16] TIA was defined as the presence of a new focal neurological deficit consistent with stroke onset lasting <24 hours and without imaging evidence of diffusion-weighted imaging scan. Vascular death referred to any sudden unexplained death and death within 1 month after the onset of cardiac event. Ischemic/hemorrhagic stroke or acute coronary syndrome resulting in death was considered to be an original cardiovascular events rather than a vascular death. All vascular outcomes and deaths were carefully reviewed and confirmed by investigators (B.-S.K and G.-M.K) who were unaware of baseline ICAS burden.

Statistical Analysis

Continuous variables were presented as mean with corresponding SD or median with corresponding interquartile range, whereas categorical variables were summarized as number and percentage. Intergroup difference was assessed by the 1-way ANOVA test or χ^2 test. Logistic regression analysis was used to determine the association between ICAS burden and LAA in patients with recurrent stroke. Cox proportional hazard regression model was used to compare the risk of clinical outcome events between the groups by ICAS burden. Covariates that were statistically significant on univariate analysis (P<0.05) were considered to be potential predictors of study outcome and were entered in multivariate models. Longitudinal association was reported as hazard ratio (HR) with corresponding 95% confidence interval (CI) for all models.

To minimize the presence of baseline differences between the groups by ICAS burden, we conducted propensity score matching.[17] Propensity scores were calculated using a logistic regression model, including age, sex, body mass index, hypertension, diabetes mellitus, hyperlipidemia, current smoking, coronary heart disease, cardioembolic source, stroke or TIA history, significant extracranial carotid atherosclerosis, stroke pathogenesis, antiplatelets, anticoagulants, and statins. Study patients were matched in a 2-phase process using nearest available matching. In the first phase, patients with advanced ICAS were 1:1 matched with those with single ICAS; in the second phase, patients with advanced ICAS were 1:2 matched with those with no ICAS based on the propensity score similarities. An absolute standardized mean difference <0.25 for the measured covariate indicated an acceptable balance between the groups.

All tests were 2 tailed, and P<0.05 was considered to be statistically significant. Statistical analyses were conducted with SPSS 18.0 (SPSS, Inc, Chicago, IL), and propensity score-matched analyses were performed using R statistics software with the Matchit package (R Foundation 207 for Statistical Computing, Vienna, Austria).

Results

Patients and Baseline Characteristics

During a 3-year period, 1265 consecutive stroke or TIA patients were enrolled in the stroke registry. We excluded 184 patients who met one or more of the following criteria: (1) incomplete clinical, laboratory, and neurovascular imaging (n=158); (2) loss to follow-up or transfer to another hospital before the 1-month visit after discharge (n=59); and (3) death during admission of index stroke (n=24). A total of 1081 patients (mean age, 63.8±12.7 years; ranging from 25–94 years; 62.4% male sex; 90.3% ischemic stroke and 9.7% TIA) were included in the study analysis. Of these, 405 (37.4%) had significant ICAS, and 185 (17.1%) were classified as having advanced ICAS. The proportions of clinically relevant ICAS were 40.5% and 51.9% in the single and advanced ICAS groups, respectively. Baseline characteristics of the groups by ICAS burden are summarized in Table 1.

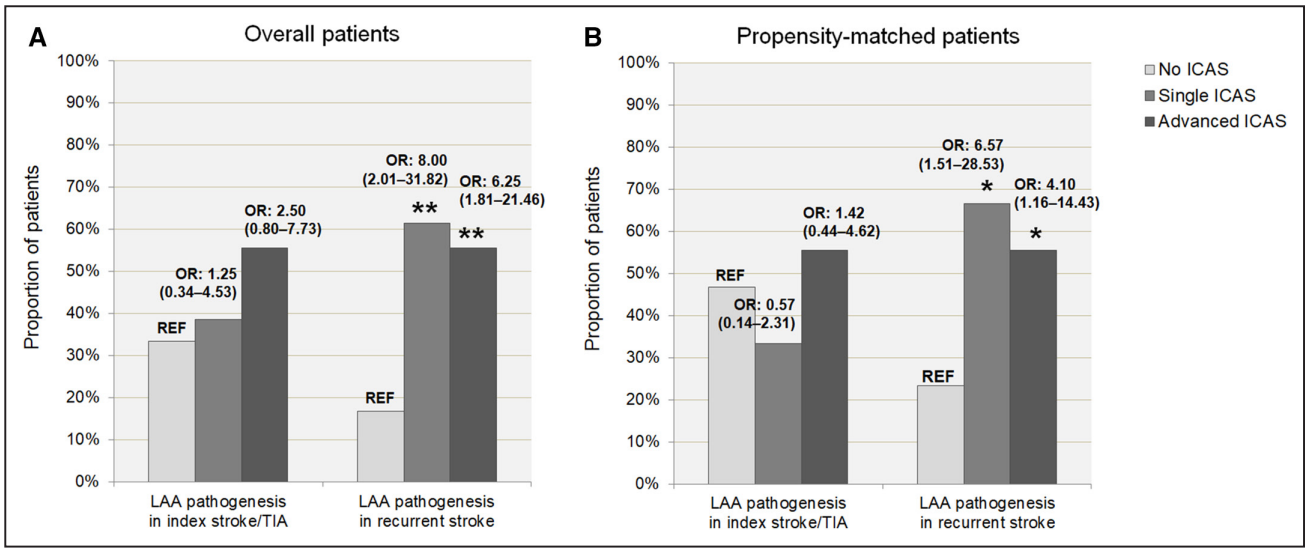

Figure 1. Proportion of patients showing large artery atherosclerosis (LAA) pathogenesis and odds ratios (ORs) with 95% confidence intervals of intracranial atherosclerosis burden with LAA pathogenesis among patients with recurrent ischemic stroke. *P* value was obtained by logistic regression analysis to assess the association of intracranial atherosclerosis burden with LAA pathogenesis (reference [REF]: no intracranial atherosclerosis [ICAS]). *P<0.05, **P<0.005. TIA indicates transient ischemic attack.

Clinical Outcome

Study patients were followed for a median of 61.1 months (interquartile range, 18.4–77.7) after the onset of index stroke/TIA. During the follow-up period, composite vascular outcome occurred in 182 patients (16.8%): ischemic stroke in 73 (6.8%), TIA in 42 (3.9%), hemorrhagic stroke in 33 (3.1%), acute coronary syndrome in 17 (1.6%), and vascular death in 17 (2.4%).

Recurrence rates of ischemic stroke and composite outcome during follow-up were reported as 6.2% and 13.8% in the no ICAS group, 5.9% and 18.2% in the single ICAS group, and 9.7% and 26.5% in the advanced ICAS group, respectively. Recurrent rates on the first occurrence of primary and secondary outcome were 3.5% and 7.2% at the first year of the follow-up and 1.4% and 3.2% at the second year of the follow-up. Among patients with recurrent ischemic stroke, the single and advanced ICAS groups were associated with LAA pathogenesis at recurrent stroke ($P<0.005$), whereas ICAS burden was not related to LAA at baseline (Figure 1). Kaplan–Meier analysis showed that the advanced ICAS group was associated with composite vascular outcome, compared with the no ICAS group (Figure 2). Univariate Cox proportional hazard analyses to identify potential predictors for primary and secondary outcome are summarized in Tables I and II in the online-only Data Supplement. Multivariate analysis adjusting for potential covariates indicated that the extent of ICAS was associated with both ischemic stroke and composite vascular outcome. The advanced ICAS group was not associated with ischemic stroke (HR, 1.56; 95% CI, 0.88–2.74; $P=0.124$) but was associated with composite vascular outcome (HR, 1.72; 95% CI, 1.17–2.53; $P=0.006$). Separate analysis for various kinds of stroke and TIA in composite vascular outcome was summarized in Tables III and IV in the online-only Data Supplement. An analysis on the association between ICAS burden stratified clinical relevance and vascular outcome were shown in Table V in the online-only Data Supplement. The extent of ICAS and advanced ICAS was significantly associated with the increased risk of TIA after adjustment of potential confounders (Table 2).

Propensity Score-Matched Analysis

All baseline covariates were well balanced between the advanced and single ICAS groups, whereas covariate of stroke pathogenesis was not sufficiently balanced between the advanced and no ICAS groups (Table 1). A total of 142 (19.3%) composite vascular outcomes occurred during follow-up:

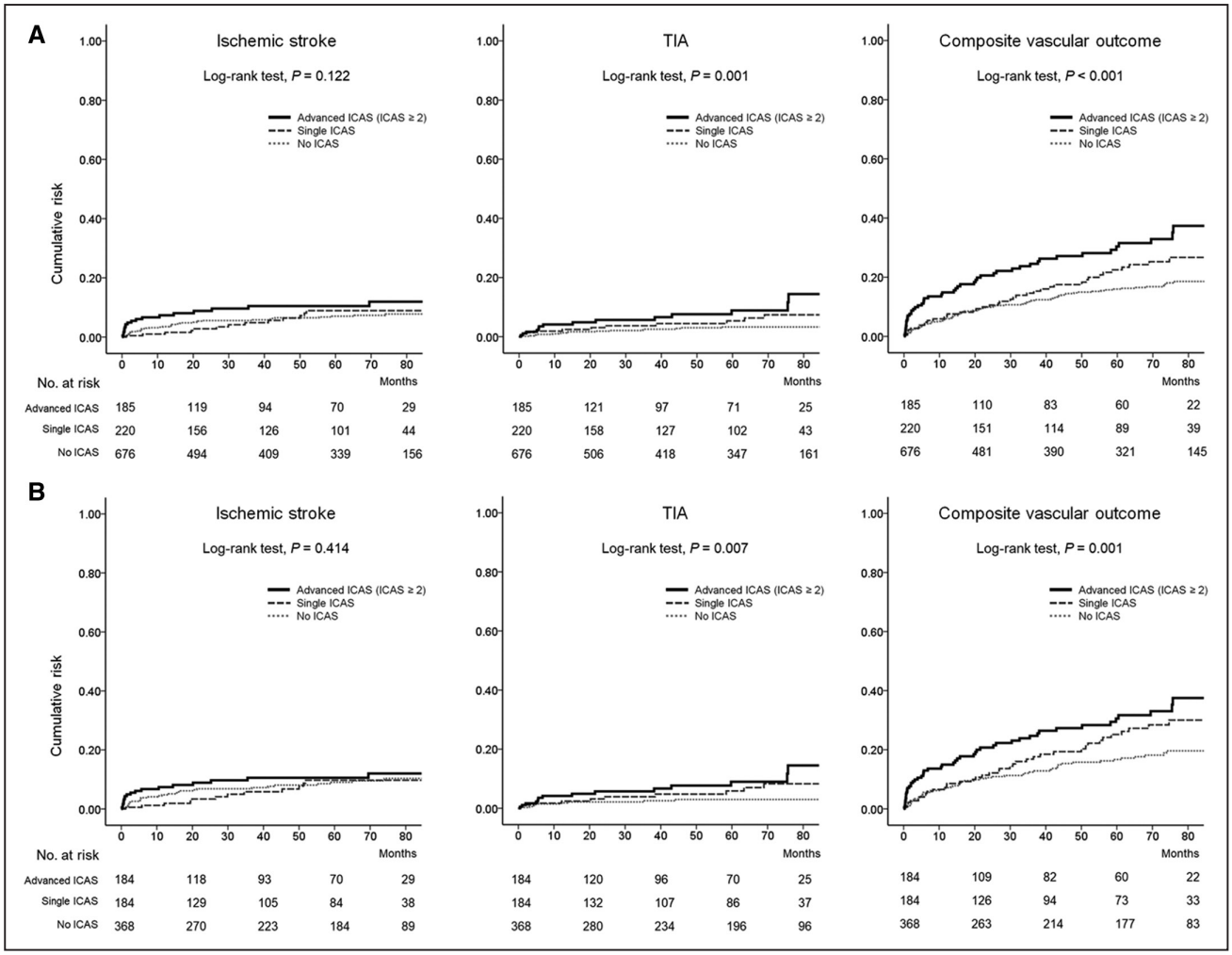

Figure 2. Kaplan–Meier analysis on the cumulative risk of recurrent ischemic stroke, transient ischemic attack (TIA), and composite vascular outcome in the (**A**) overall and (**B**) propensity-matched patients. ICAS indicates intracranial atherosclerosis.

Table 2. Multivariable Adjusted HRs of ICAS Burden for Recurrent Ischemic Stroke, Transient Ischemic Attack, and Composite Vascular Outcome in the Overall and Propensity-Matched Patients

	Overall Patients						Propensity-Matched Patients					
	Ischemic Stroke		TIA		Composite Vascular Outcome		Ischemic Stroke		TIA		Composite Vascular Outcome	
	HR (95% CI)*	*P* Value	HR (95% CI)†	*P* Value	HR (95% CI)‡	*P* Value	HR (95% CI)§	*P* Value	HR (95% CI)‖	*P* Value	HR (95% CI)¶	*P* Value
Per 1 increase of ICAS	1.19 (1.01–1.42)	0.042	1.26 (1.00–1.58)	0.047	1.18 (1.05–1.33)	0.007	1.13 (0.94–1.36)	0.190	1.31 (1.05–1.64)	0.017	1.20 (1.06–1.36)	0.004
ICAS category												
No ICAS	reference		reference		reference		reference		reference		reference	
Single ICAS	0.92 (0.49–1.73)	0.800	1.60 (0.72–3.55)	0.245	1.08 (0.73–1.62)	0.693	0.77 (0.39–1.51)	0.450	2.33 (0.93–5.83)	0.071	1.28 (0.82–1.98)	0.269
Advanced ICAS (ICAS≥2)	1.56 (0.88–2.74)	0.124	2.48 (1.11–5.52)	0.026	1.72 (1.17–2.53)	0.006	1.28 (0.71–2.30)	0.407	3.41 (1.43–8.12)	0.005	1.95 (1.27–2.99)	0.002
P for trend		0.185		0.025		0.009		0.519		0.005		0.002
Subcategory of advanced ICAS												
By number												
ICAS=2	1.15 (0.53–2.50)	0.719	2.10 (0.81–5.46)	0.127	1.64 (1.03–2.61)	0.037	1.02 (0.46–2.25)	0.947	2.96 (1.07–8.16)	0.036	1.93 (1.17–3.18)	0.009
ICAS≥3	2.12 (1.05–4.27)	0.034	3.05 (1.16–7.98)	0.023	1.83 (1.10–3.03)	0.019	1.58 (0.77–3.26)	0.207	4.03 (1.46–11.09)	0.007	1.97 (1.15–3.40)	0.014
By distribution												
Single circulation	0.84 (0.33–2.15)	0.722	2.86 (1.11–7.39)	0.029	1.53 (0.93–2.52)	0.095	0.71 (0.27–1.85)	0.493	4.19 (1.53–11.42)	0.005	1.83 (1.06–3.13)	0.028
Both circulation	2.35 (1.23–4.48)	0.010	2.15 (0.79–5.79)	0.130	1.91 (1.19–3.05)	0.007	1.84 (0.95–3.55)	0.070	2.80 (0.98–7.98)	0.054	2.06 (1.25–3.38)	0.004

Variables with $P<0.05$ in univariate analysis were entered in multivariate models. CI indicates confidence interval; ECCAS, extracranial carotid atherosclerosis; HR, hazard ratio; ICAS, intracranial atherosclerosis; and TIA, transient ischemic attack.

*Adjusted for age, current smoking, previous stroke/TIA, ECCAS ≥50%, anticoagulants, and statin.

†Adjusted for diabetes mellitus, dyslipidemia, previous stroke/TIA, ECCAS ≥50%, and stroke pathogenesis.

‡Adjusted for age, body mass index, dyslipidemia, previous stroke/TIA, ECCAS ≥50%, stroke pathogenesis, antiplatelets, anticoagulants, and statin.

§Adjusted for current smoking, previous stroke/TIA, ECCAS ≥50%, and anticoagulants.

‖Adjusted for dyslipidemia, ECCAS ≥50%, and stroke pathogenesis.

¶Adjusted for age, dyslipidemia, cardioembolic source, previous stroke/TIA, ECCAS ≥50%, stroke pathogenesis, antiplatelets, anticoagulants, and statin.

ischemic stroke in 60 (8.2%) patients, TIA in 33 (4.5%), hemorrhagic stroke in 20 (2.7%), acute coronary syndrome in 16 (2.2%), and vascular death in 13 (1.7%). The cumulative risks of TIA and composite vascular outcome were higher for the advanced ICAS group than for the no ICAS group (Figure 2). In multivariate Cox proportional hazard analyses, advanced ICAS was associated with the risk of both TIA (HR, 3.41; 95% CI, 1.43–8.12; P=0.005) and composite vascular outcome (HR, 1.95; 95% CI, 1.27–2.99; P=0.002; Table 2).

Subgroup Analysis of Risk of Advanced ICAS for Clinical Outcome

We conducted subgroup analysis to determine whether the risks of advanced ICAS for composite vascular outcome were consistent across various clinical subgroups; calculated unadjusted HRs for composite vascular outcome in the overall and propensity-matched patients are shown in Figure 3. The association between study outcome and advanced ICAS was observed in various subgroups.

Discussion

In this study, the risk for clinical vascular outcome was increased according to ICAS burden and the extent of distribution. Advanced ICAS did not increase the risk of ischemic stroke alone but was associated with the risk of TIA and composite vascular outcome. These results were maintained in the propensity-matched patients. Moreover, the association was consistent across various clinical subgroups. Despite the fact that ICAS is an atherosclerotic disease of the brain, the primary findings suggest that its burden can reflect the risk of long-term vascular outcome.

With growing interest in ICAS, many studies have been conducted to identify the risk of ICAS for recurrent stroke and major vascular outcome. Exact implications and meanings differ somewhat because of variations in participants (patients with stroke versus general population), clinical relevance of ICAS (only symptomatic lesion versus overall ICAS, including both symptomatic and asymptomatic lesions), definition and measurement of ICAS, baseline stroke pathogenesis of

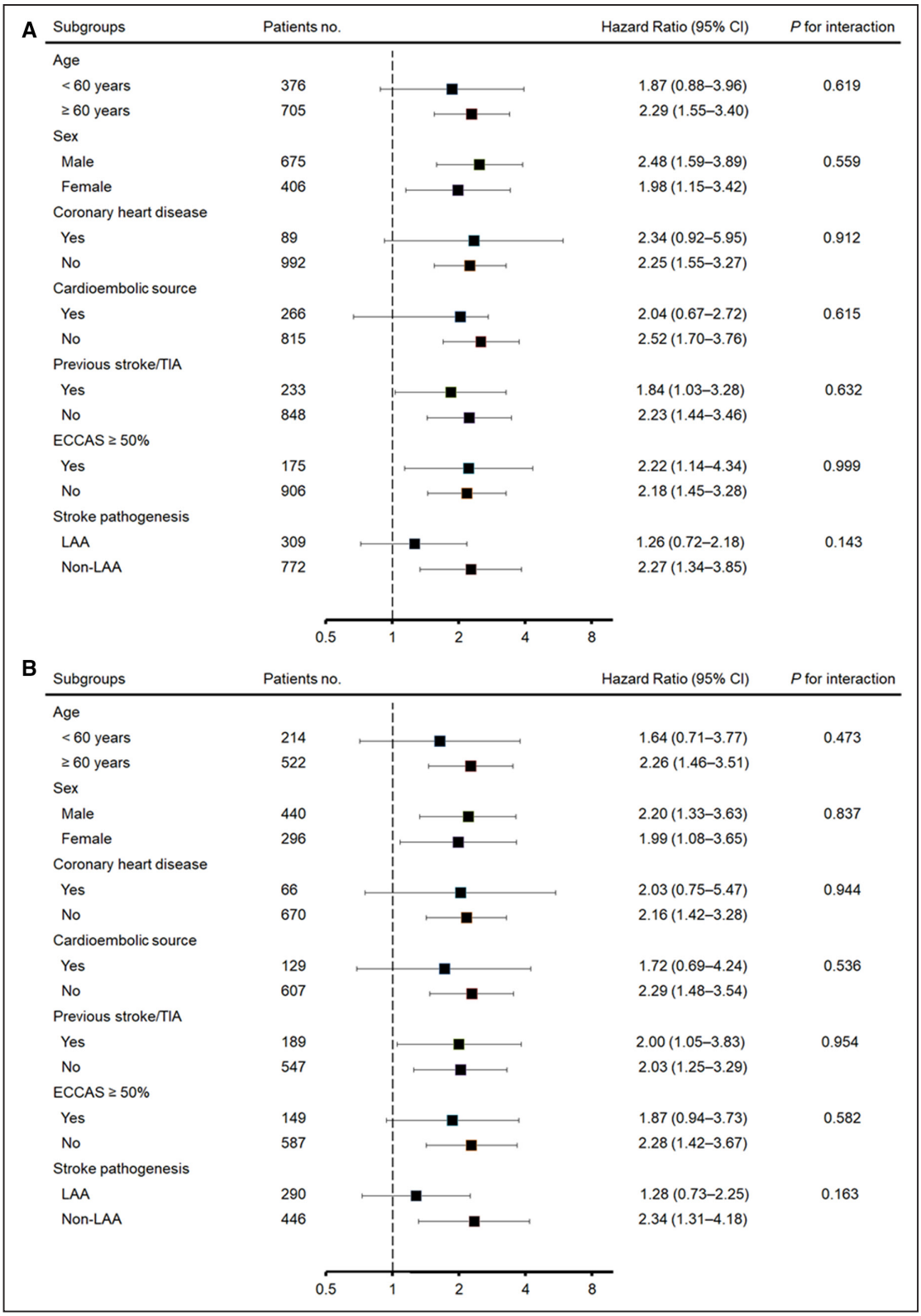

Figure 3. Stratified analysis: comparative unadjusted hazard ratios of advanced intracranial atherosclerosis for composite vascular outcome for subgroups in the (**A**) overall and (**B**) propensity-matched patients. CI indicates confidence interval; ECCAS, extracranial carotid atherosclerosis; LAA, large artery atherosclerosis; and TIA, transient ischemic attack.

participants (only ICAS-related stroke versus overall ischemic stroke), study outcome (recurrent stroke versus major vascular outcome), follow-up period, management for secondary prevention (best medical treatment versus intracranial stenting), and race of participants among studies.[9–11,18–24] Moreover, a few studies have investigated whether ICAS burden could be

a predictor of major clinical events in patients with ischemic stroke during a long-term period.[9–11] Although the results from these studies were largely consistent with our findings, the clinical significance of ICAS has not yet been determined in terms of various characteristics of patients with ischemic stroke (ie, non-LAA stroke pathogenesis, significant extracranial carotid atherosclerosis, and potential cardioembolic source). Notably, our data indicate that advanced ICAS predicts future vascular outcome beyond those potential risk factors. In addition, the vascular risk of coexisting ICAS has rarely been characterized in patients with non-LAA stroke, despite the fact that non-LAA usually accounts for ≤3-quarters of the stroke pathogenesis in ischemic stroke.[25] The subgroup analysis demonstrated that coexisting advanced ICAS was related to the risk of vascular outcome in patients with non-LAA stroke. In this regard, we may need to pay more attention to ICAS burden in patients with ischemic stroke in daily clinical practice, even if their index stroke was not because of LAA pathogenesis or their ICAS seems to be of no concern at baseline.

Patients with higher ICAS burden were likely to have a higher burden of vascular risk factors than those with single ICAS or without ICAS.[1,2] A higher rate of recurrent vascular outcome in patients with higher ICAS burden may be attributed to a high burden of vascular risk factors rather than ICAS burden. We conducted propensity score-matched analysis to confirm whether ICAS burden was associated with subsequent vascular outcome when differences in baseline characteristics between the ICAS burden groups were reduced. Similar results were observed in propensity-matched patients. Therefore, ICAS burden should be considered not only a vascular finding caused by conventional risk factors but also an independent risk factor for long-term vascular outcome in patients with ischemic stroke. This is consistent with a previous report that imaging biomarkers may be beneficial to improve risk stratification for recurrent stroke in the clinical care of patients with ischemic stroke.[26]

In the present study, among the patients with recurrent ischemic stroke, LAA was the distinctively prevalent pathogenesis of clinical recurrence in patients with ICAS compared with those without. However, the proportion of LAA in the advanced ICAS group was not higher than that in the single ICAS group (55.6% versus 61.5%). Of the patients with recurrent stroke with advanced ICAS, undetermined cause was the most common non-LAA pathogenesis (16.7%). One possible explanation for this is that another atherosclerotic cause, such as mild ICAS (<50% stenosis) or aortic arch atheroma, may play a role in stroke recurrence of patients with advanced ICAS.[3,25] In this regard, these possible cases may be classified as undetermined cause in our study. Because our data did not extensively cover those emerging embolic sources, further studies are required to confirm our finding.

There are several limitations in our study that should be mentioned. First, we defined significant ICAS as ≥50% stenosis or occlusion of intracranial large arteries based on angiographic data. Such assessment is one of the most commonly used methods to diagnose ICAS in both research and clinical fields; however, it lacks pathological evidence. Therefore, we cannot ignore the possibility that various nonatherosclerotic steno-occlusions may be mistakenly classified as ICAS. Second, we did not consider significant stenosis located in the distal intracranial arteries; this underestimation could lower the internal validity of the main measure (ICAS burden). Third, this was not a prospective study, and unmeasured confounders may exist. In our study, initial neurological severity, the NIH stroke scale, and intracranial calcification were not included in the analysis because these factors were not available for all study patients. Future prospective studies should include those variables in the analysis. Fourth, although ICAS with hemodynamic compromise or unstable plaque may have greater risk for future vascular outcome, we only defined ICAS burden as number of cerebral arteries with ICAS. Fifth, the decision on secondary stroke prevention may be influenced by ICAS status because the treating neurologists were not blinded to initial angiographic data. The advanced ICAS group received more antiplatelet and statin therapy; nonetheless, the risk of ICAS for clinical events remained significant after adjustment for secondary stroke prevention. Finally, our study enrolled patients who were predisposed to ICAS; therefore, the results should be interpreted with caution and cannot easily be generalized to other races.

Conclusions

The ICAS burden was longitudinally associated with an increased risk of subsequent vascular outcome in patients with ischemic stroke, suggesting that ICAS burden is an independent risk factor. ICAS burden was associated with LAA pathogenesis in recurrent stroke. Individualized and comprehensive management considering these findings might be needed to reduce the risk of recurrent vascular outcome in patients with ICAS burden.

Disclosures

None.

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