

Left Atrial Size and Long-Term Risk of Recurrent Stroke After Acute Ischemic Stroke in Patients With Nonvalvular Atrial Fibrillation

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Background—Among patients with ischemic stroke and atrial fibrillation, which ones are at high risk of recurrent stroke is unclear. This study aimed to determine whether left atrial size was associated with long-term risk of stroke recurrence in patients with nonvalvular atrial fibrillation.

Methods and Results—In this multicenter prospective cohort study, nonvalvular atrial fibrillation patients hospitalized for acute ischemic stroke were enrolled and followed up after discharge. Indexed-left atrial diameter was obtained by dividing left atrial diameter by body surface area. Cause-specific and subdistribution hazard ratios of recurrent stroke were estimated by Cox proportional hazards and Fine–Gray models, respectively. Risk prediction was evaluated by integrated discrimination improvement and net reclassification improvement. In total, 1611 patients (77.8 ± 10.2 [mean \pm SD] years, 44.5% female) were included. During follow-up for 2.40 ± 1.63 (mean \pm SD) years, 251 patients had recurrent stroke and 514 patients died. An increased indexed-left atrial diameter (per 1 cm/m²) was significantly associated with elevated risk of stroke recurrence (hazard ratio 1.60, 95% CI 1.30–1.98). The association was maintained when death was regarded as the competing risk and in 1464 patients who were treated with anticoagulants (hazard ratio 1.59, 95% CI 1.27–2.00). Risk prediction for recurrent stroke was significantly improved by adding indexed-left atrial diameter to the baseline model composed of the factors in the CHADS₂ score or those in the CHA₂DS₂-VASc score.

Conclusion—These findings suggest that left atrial enlargement is associated with an increased risk of recurrent stroke in nonvalvular atrial fibrillation patients with ischemic stroke. (*J Am Heart Assoc.* 2017;6:e006402. DOI: 10.1161/JAHA.117.006402.)

Key Words: atrial fibrillation • ischemic stroke • left atrial diameter • recurrent event

Atrial fibrillation is the most common sustained cardiac rhythm disorder, and its frequency increases with age.¹ Atrial fibrillation is a well-known risk factor for thromboembolism and a predominant cause of cardioembolic stroke. In

patients with nonvalvular atrial fibrillation (NVAf) who do not receive anticoagulation therapy, the risk of stroke or systemic thromboembolism can be estimated by using risk scores, such as the CHADS₂ score² and CHA₂DS₂-VASc score,³ which account for risk factors including age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases. A further risk score, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score, was also developed and validated for the prediction of stroke in patients with atrial fibrillation.^{4,5} Regarding the prediction of stroke in NVAf patients undergoing anticoagulation therapy, biomarker-based risk scores have been recently proposed.^{6–10}

In patients with sinus rhythm, left atrial diameter (LAD) was shown to predict a future occurrence of atrial fibrillation.^{11–13} Additionally, in the general population^{14–16} as well as in patients with stroke of all subtypes,¹⁷ LAD was reported to be a predictor of cardiovascular events even after adjustment for atrial fibrillation. Therefore, LAD is expected to be a suitable marker for the prediction of future cardiovascular risk in NVAf patients. However, in patients with atrial fibrillation, various results have been reported thus far regarding LAD as a cardiovascular risk factor. Some studies showed a positive

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Accompanying Tables S1 through S3 and Figures S1, S2 are available at <http://jaha.ahajournals.org/content/6/8/e006402/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- Left atrial enlargement was a predictor of stroke recurrence in nonvalvular atrial fibrillation patients with prior ischemic stroke independently of other risk factors and anticoagulation therapy.

What Are the Clinical Implications?

- A simple measurement of left atrial diameter provides clinically useful information on the future risk of recurrent stroke in nonvalvular atrial fibrillation patients undergoing anticoagulation therapy.

association between LAD and cardiovascular events,^{18–22} whereas others found no obvious association.^{23–28}

In this study, we hypothesized that left atrial size may be useful to predict the future incidence of recurrent stroke in NVAF patients with ischemic stroke. To test this hypothesis, we performed a multicenter prospective cohort study that enrolled NVAF patients with acute ischemic stroke. Additionally, patients were followed up after discharge. The aim of this study was to determine whether left atrial size is associated with the risk of stroke recurrence in patients with NVAF and ischemic stroke.

Methods

Study Design

The Fukuoka Stroke Registry is a multicenter hospital-based study in which patients with acute stroke are prospectively enrolled within 7 days of stroke onset (UMIN Clinical Trial Registry 00000800). Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka-Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Steel Memorial Yawata Hospital, and Japan Labor Health and Welfare Organization Kyushu Rosai Hospital in Fukuoka, Japan participate in this registry.^{29,30} The institutional review committee of each hospital approved the study protocol. Written informed consent was obtained from all participants. Stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficit persisting more than 24 hours. Ischemic stroke was diagnosed by using computed tomography or magnetic resonance imaging.

Participants

Among stroke patients in the Fukuoka Stroke Registry between June 2007 and September 2014, 2062 patients

diagnosed with ischemic stroke by means of computed tomography or magnetic resonance imaging with diffusion-weighted magnetic resonance imaging also had atrial fibrillation. Atrial fibrillation was diagnosed based on electrocardiography during the index hospitalization or previous medical history. Paroxysmal, persistent, or permanent atrial fibrillation was considered atrial fibrillation. Of 2062 patients with ischemic stroke and atrial fibrillation, 38 patients with mitral valve stenosis or mechanical valve replacement, 240 patients in whom accurate data on LAD could not be obtained by transthoracic echocardiography, and 141 patients who had stroke or died during their hospitalization were excluded. Thus, we enrolled 1643 NVAF patients with ischemic stroke in this study. Among patients who initially agreed and gave consent to participate, 32 were lost to follow-up. Finally, information regarding events of interest was obtained for the remaining 1611 patients (Figure S1).

Baseline Characteristics

We investigated baseline characteristics during the index hospitalization, including hypertension, diabetes mellitus, chronic heart disease, and vascular diseases. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg in the chronic stage, or as a previous history of treatment with antihypertensive drugs. Diabetes mellitus (chronic stage) was determined by either the diagnostic criteria of the Japan Diabetes Society³¹ or based on medical history of diabetes mellitus. Chronic heart failure was defined as the presence of symptoms typical of heart failure (breathlessness at rest or during exercise, fatigue, tiredness, ankle swelling), signs typical of heart failure (tachycardia, tachypnea, pulmonary rales, pleural effusion, increased jugular venous pressure, peripheral edema, hepatomegaly), and objective evidence of a structural or functional cardiac abnormality at rest (cardiomegaly, third heart sound, cardiac murmurs, echocardiographic abnormality, and increased natriuretic peptide concentration).³² Vascular diseases included ischemic heart diseases and peripheral arterial diseases. Ischemic heart disease included angina pectoris, myocardial infarction, and intervention or bypass surgery for coronary artery diseases before or during the hospitalization. Peripheral arterial disease was defined as history of or current intermittent claudication caused by arterial stenosis. Chronic kidney disease was defined as an estimated glomerular filtration rate of < 60 mL/min per 1.73 m², whereby estimated glomerular filtration rate was determined using the equation proposed by the Japanese Society of Nephrology as follows: estimated glomerular filtration rate (mL/min per 1.73 m²) = $194 \times (\text{serum creatinine [mg/dL]})^{-1.094} \times \text{age [years]} - 0.287 \times 0.739$ (if female).³³ Although all patients had ischemic stroke at enrollment, we

additionally investigated the history of any types of stroke before the index ischemic stroke. If we additionally identified causes of ischemic stroke other than fibrillation, such as large artery atherosclerosis, small vessel diseases, or other miscellaneous causes, we defined them as other potential causes for stroke.³⁴ Functional outcome was assessed by the modified Rankin Scale at discharge. Pre- or poststroke anticoagulation therapy was defined as oral anticoagulants prescribed before onset or at discharge, respectively. Oral anticoagulants included warfarin and direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban).

Measurement of Indexed-LAD

The anteroposterior diameter of the left atrium was measured in the end systole, from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall in the parasternal long-axis view by using transthoracic echocardiography.³⁵ To standardize the value of LAD, we calculated indexed-LAD (LADi) by dividing LAD (cm) by body surface area (m²). Body surface area (m²) was calculated as $88.83 \times [\text{weight (kg)}]^{0.444} \times [\text{height (m)}]^{0.663}$, which was developed specifically for the estimation of the body surface area of Japanese individuals.³⁶

Follow-Up

The mean (\pm SD) length of hospitalization was 27 ± 17 days, and the index date was the date of discharge. After discharge, patients were followed up in person or through family members who consented to answer questions regarding the health status of patients by telephone interviews at 3, 6, and 12 months after the onset of stroke, and yearly thereafter. For each event, patients or their family members were interviewed by trained research nurses, who were masked to the clinical data of patients, using a standardized interview form. Information about the occurrence of all study outcomes of interest and the treatments that each patient underwent were collected. All event information was reviewed by the event adjudication committee members, who were masked to the clinical background of patients. When the committee suspected that a primary or secondary outcome occurred by reviewing the interview records, additional information was obtained from hospitals or other healthcare providers as needed.

Study Outcomes

The primary outcome was stroke recurrence, which included both ischemic and hemorrhagic stroke during follow-up. Hemorrhagic stroke included intracerebral hemorrhage and subarachnoid hemorrhage. The secondary outcomes were

death from any cause, recurrence of ischemic stroke, and hemorrhagic stroke.

Statistical Analysis

Patients were categorized into 4 groups according to the quartile of LADi, and the trends in their baseline characteristics were analyzed using the Jonckheere–Terpstra test or the Cochran–Armitage test. Cumulative event rates were calculated by the Kaplan–Meier method. Cause-specific hazard ratios were evaluated by a Cox proportional hazards model. Data were censored at the time of the first relevant outcome, the date of patient's death, or the date of patient's last follow-up. The Cox model included age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases. Hazard ratios and 95% CIs of the second (Q2), third (Q3), and top quartiles (Q4) with reference to the bottom quartile (Q1) of LADi or per 1 cm/m² increase in LADi were assessed. The proportional hazards assumption was tested by log-log survival plots. For the sensitivity analysis, chronic kidney disease, history of stroke before the index ischemic stroke, modified Rankin Scale at discharge, and poststroke anticoagulation therapy were additionally included in the multivariable model. These variables were selected according to their clinical significance and the possibility of confounding. The Fine–Gray model was also used to evaluate subdistribution hazard ratios of recurrent stroke by regarding death as a competing risk.³⁷ Subgroup analysis was performed by age (≥ 80 or < 80 years), sex (women or men), hypertension (yes or no), diabetes mellitus (yes or no), vascular diseases (yes or no), and chronic heart failure (yes or no). The heterogeneity of the association of LADi with outcomes in each subgroup was tested by adding an interaction term to the relevant Cox models.

To determine whether LADi contributed to the improvement of risk prediction, we further evaluated c-statistics, integrated discrimination improvement, and net reclassification improvement for the survival data.^{38–40} The estimated risk of recurrent stroke for 5 years of follow-up was calculated from a Cox model. The baseline risk prediction model was composed of the factors in the CHADS₂ score or CHA₂DS₂-VASc score. Integrated discrimination improvement, and noncategorical net reclassification improvement evaluated the improvement of the predicted probabilities and the correctness of reclassification, respectively, using a new model by adding LADi to the baseline model.^{39,40} CIs of c-statistics, integrated discrimination improvement, and net reclassification improvement were calculated by bootstrap resampling. Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC). All tests were 2-sided, and a *P* value of < 0.05 was considered to be statistically significant.

Results

Baseline Characteristics of the Patients

Patients had a mean (\pm SD) age of 77.8 ± 10.2 years, and 717 patients (44.5%) were female. The mean (\pm SD) size of LADi was 2.83 ± 0.62 cm/m². Table 1 shows the clinical background of patients in the overall cohort according to quartiles of LADi. Patient age tended to increase with increasing LADi. Additionally, female sex and chronic heart failure were more prevalent with increasing LADi, whereas the frequency of diabetes mellitus decreased as LADi increased.

LADi and Recurrent Stroke

The mean (\pm SD) follow-up time was 2.40 ± 1.63 years, and total follow-up time of the overall cohort was 3870 patient-years. During the follow-up period, 251 patients had recurrent stroke and 514 patients died. Cumulative event-free rates for stroke recurrence (Figure A) and those for stroke or death (Figure B) decreased in patients with larger LADi. We then used a Cox proportional hazards model to adjust for factors included in the CHA₂DS₂-VASc score (ie, age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases). Consequently, hazard ratios of stroke recurrence increased significantly and linearly according to the LADi quartile (Table 2).

LADi and Secondary Outcomes

The cumulative incidence and hazard ratios for the secondary outcomes were also compared according to LADi (Table S1). During follow-up, the hazard ratio of death showed an increasing trend with increasing LADi. Ischemic stroke occurred in 219 patients, and the cumulative incidence of ischemic stroke and the hazard ratio also significantly increased with LADi. By contrast, hemorrhagic stroke showed no significant difference in hazard ratios according to LADi.

Subgroup Analysis

A subgroup analysis was performed to elucidate whether there was heterogeneity in the association between LADi and stroke recurrence according to patient background characteristics. As a result, we found no evidence that the association differed according to subgroups by sex, hypertension, diabetes mellitus, vascular diseases, and chronic heart failure (Figure S2). When we further included other variables in the multivariable model, such as chronic kidney disease, history of stroke before the index stroke, modified Rankin Scale at discharge, poststroke anticoagulation therapy, paroxysmal atrial fibrillation, and other potential causes for ischemic stroke, no interactions between LADi and these variables were found (*P* for heterogeneity >0.2).

Table 1. Baseline Characteristics According to LADi

	Q1, n=405 LADi <2.40	Q2, n=405 2.40 ≤ LADi <2.76	Q3, n=401 2.76 ≤ LADi <3.19	Q4, n=400 3.19 ≤ LADi	<i>P</i> for Trend
Age, y (mean \pm SD)	74.1 \pm 10.7	75.5 \pm 9.9	79.5 \pm 9.1	82.2 \pm 8.9	<0.001
Female, n (%)	82 (20.3)	137 (33.8)	202 (50.4)	296 (74.0)	<0.001
Risk factors, n (%)					
Hypertension	302 (74.6)	320 (79.0)	326 (81.3)	308 (77.0)	0.30
Diabetes mellitus	113 (27.9)	90 (22.2)	105 (26.2)	69 (17.3)	0.003
Vascular diseases	82 (20.3)	97 (24.0)	100 (24.9)	89 (22.3)	0.45
Ischemic heart disease	70 (17.3)	80 (19.8)	83 (20.7)	71 (17.8)	0.78
Peripheral arterial disease	20 (4.9)	26 (6.4)	29 (7.2)	26 (6.5)	0.31
Chronic heart failure	37 (9.1)	56 (13.8)	71 (17.7)	134 (33.5)	<0.001
Chronic kidney disease	164 (40.5)	183 (45.2)	208 (52.0)	208 (52.1)	<0.001
Paroxysmal atrial fibrillation, n (%)	266 (65.7)	207 (51.1)	145 (36.2)	101 (25.3)	<0.001
Recurrent stroke, n (%)	74 (18.3)	78 (19.3)	80 (20.0)	105 (26.3)	0.01
Other potential causes for ischemic stroke, n (%)	110 (27.2)	75 (18.5)	83 (20.7)	63 (15.8)	<0.001
Modified Rankin scale at discharge, median (IQR)	3 (1–4)	2 (1–4)	3 (1–4)	3 (1–4)	<0.001
Poststroke anticoagulation therapy, n (%)	363 (89.6)	374 (92.4)	371 (92.5)	356 (89.0)	0.79

IQR indicates interquartile range; LADi, left atrial diameter index; Q1 to Q4, quartiles of left atrial diameter index (cm/m²).

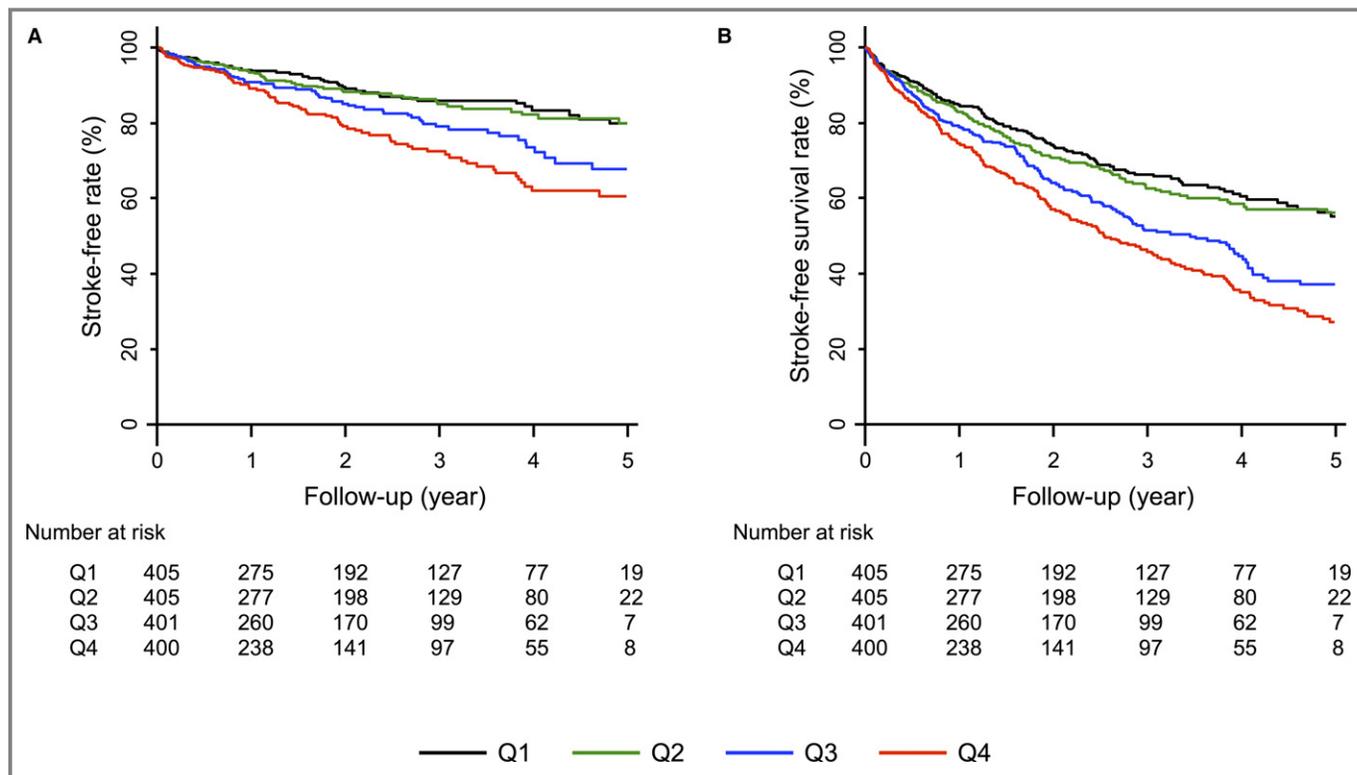


Figure. Cumulative event-free rate of stroke and composite of stroke or death according to quartile of LADi. Cumulative event-free rate of recurrent stroke (A) and stroke or death (B) were shown according to quartile of LADi. Patients were divided into 4 groups according to quartile of LADi. LADi indicates left atrial diameter index; Q1 to Q4, quartiles of LADi.

Sensitivity Analyses

To exclude the possible involvement of other factors, we further adjusted for potentially confounding factors, including chronic kidney disease, history of stroke before index ischemic stroke, modified Rankin Scale at discharge, and anticoagulation therapy (Table 3). However, the association between LADi and recurrent stroke was unchanged. When death was regarded as the competing risk, subdistribution hazard ratios showed the same trends as cause-specific hazard ratios for recurrent stroke (Table 3). Furthermore, in 1464 patients who received anticoagulation therapy, similar trends for cause-specific hazard ratios of recurrent stroke were maintained (Table 4).

Predictive Ability of LADi

Finally, we investigated whether LADi improved risk prediction of recurrent stroke (Table 5). Compared with a predictive model composed of the factors of the CHADS₂ score (ie, age, hypertension, chronic heart failure, and diabetes mellitus), addition of LADi to the model significantly improved the c-statistics, integrated discrimination improvement, and continuous net reclassification improvement. Similarly, LADi significantly improved the predictive ability for recurrent

stroke even when the factors of the CHA₂DS₂-VASc score (ie, age, sex, hypertension, chronic heart failure, diabetes mellitus, and vascular diseases) were included in the baseline model.

Discussion

The major findings of this study were as follows. (1) LADi was associated with increased risk of stroke recurrence even under anticoagulation therapy or when death was regarded as a competing risk. (2) There was no heterogeneity in the association between LADi and recurrent stroke according to the risk factors assessed in the CHA₂DS₂-VASc score. (3) LADi improved risk prediction of recurrent stroke compared with the factors in the CHADS₂ score or those in the CHA₂DS₂-VASc score.

Whether LAD can be regarded as a predictor of stroke risk in NVAF patients remains unclear. A positive association between LAD and occurrence of stroke was mainly found in former studies that included small samples of patients with atrial fibrillation.^{18–22} A recent prospective study with 2334 patients with atrial fibrillation, the AFFIRM study (Atrial Fibrillation Follow-Up Investigation of Rhythm Management), could not demonstrate a positive association between these 2 factors.²⁸ There may be some possible explanations for this

Table 2. Hazard Ratios of Recurrent Stroke According to LADi

	Events (%)	Event Rate Per 100 Patient-Y	Age- and Sex-Adjusted			Multivariable-Adjusted		
			HR	95% CI	P Value	HR	95% CI	P Value
LADi quartile								
Q1 (LADi <2.40), n=405	47 (11.6)	5.0	1.00	Reference		1.00	Reference	
Q2 (2.40 ≤ LADi <2.76), n=405	50 (12.3)	5.2	1.03	0.69 to 1.54	0.87	1.06	0.71 to 1.59	0.77
Q3 (2.76 ≤ LADi <3.19), n=401	68 (17.0)	8.1	1.41	0.96 to 2.06	0.08	1.43	0.98 to 2.10	0.06
Q4 (3.19 ≤ LADi), n=400	86 (21.5)	11.1	1.81	1.23 to 2.66	0.003	1.95	1.32 to 2.88	<0.001
P for trend					<0.001			<0.001
LADi per 1 cm/m ²	251 (15.6)	7.1	1.51	1.23 to 1.86	<0.001	1.60	1.30 to 1.98	<0.001

Event rate was calculated as number of events per 100 patient-y. The multivariable model included age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases. HR indicates hazard ratio; LADi, left atrial diameter index; Q1 to Q4, quartiles of left atrial diameter index (cm/m²).

discrepancy, such as sample size, study design (retrospective case-control, or prospective cohort studies), potential confounders, and subject heterogeneity (inclusion or exclusion of rheumatic and valvular heart disease). Our study clearly indicates that LAD is an independent predictor of stroke recurrence in a substantial number of NVAF patients with prior ischemic stroke.

The present study suggests that ischemic stroke may still develop in NVAF patients with a large left atrium irrespective of potentially confounding factors and anticoagulation therapy. Previous studies showed that left atrial enlargement was associated with left atrial spontaneous echo contrast.⁴¹⁻⁴³ Moreover, Ayrala et al reported that a larger left atrial volume index was a significant predictor of the presence of left atrial appendage thrombus in 334 patients with atrial fibrillation undergoing transesophageal echocardiography before cardioversion.⁴⁴ Therefore, left atrial enlargement probably contributes to thrombogenesis via blood stasis in the left atrium, consequently increasing the risk of thromboembolic

events. In our study, PT-INR was higher at the onset of the index stroke as the LAD size increased, since anticoagulants were more frequently prescribed before the index stroke with increasing LADi (Table S2). Nevertheless, spontaneous echo contrast and D-dimer levels were still higher as LADi increased. Thus, appropriate anticoagulation is highly recommended, especially for NVAF patients with left atrial enlargement. The range of anticoagulation that is optimal for preventing recurrent stroke in patients with large left atrium remains to be clarified.

Recently, research has focused on the clinical significance of biomarkers to improve risk stratification for stroke in patients with atrial fibrillation.⁴⁵ Among them, N-terminal pro-B-type natriuretic peptide may be a promising marker for improving stroke prediction in atrial fibrillation.^{6,9,46} Since N-terminal pro-B-type natriuretic peptide levels correlate positively with left atrial volume, increased levels of N-terminal pro-B-type natriuretic peptide may at least partially reflect atrial dysfunction.⁴⁷ Our study suggests that a simple

Table 3. Hazard Ratios of Recurrent Stroke According to LADi With Different Models

	Model 1			Model 2			Model 3		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
LADi quartile									
Q1 (LADi <2.40), n=405	1.00	Reference	...	1.00	Reference	...	1.00	Reference	...
Q2 (2.40 ≤ LADi <2.76), n=405	1.01	0.68 to 1.52	0.95	1.05	0.71 to 1.57	0.80	0.99	0.66 to 1.49	0.98
Q3 (2.76 ≤ LADi <3.19), n=401	1.23	0.82 to 1.83	0.32	1.43	0.97 to 2.11	0.07	1.20	0.80 to 1.80	0.38
Q4 (3.19 ≤ LADi), n=400	1.58	1.05 to 2.39	0.03	1.91	1.30 to 2.82	0.001	1.52	1.01 to 2.28	0.04
P for trend			0.02			<0.001			0.03
LADi per 1 cm/m ²	1.45	1.15 to 1.82	0.002	1.55	1.26 to 1.90	<0.001	1.40	1.12 to 1.75	0.003

Cox model was used to estimate hazard ratio in model 1. In models 2 and 3, the subdistribution hazard ratio was estimated by regarding death as a competing risk by Fine-Gray model. Model 2 included age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases. Multivariable models 1 and 3 further included chronic kidney disease, history of stroke before the index stroke, modified Rankin scale at discharge, poststroke anticoagulation therapy, paroxysmal atrial fibrillation, and other potential causes of ischemic stroke in addition to model 2. HR indicates hazard ratio; LADi, left atrial diameter index; Q1 to Q4, quartiles of left atrial diameter index (cm/m²).

Table 4. Hazard Ratios of Recurrent Stroke According to LADi in Anticoagulated Patients

	Events (%)	Event Rate Per 100 Patient-Y	Age- and Sex-Adjusted			Multivariable-Adjusted		
			HR	95% CI	P Value	HR	95% CI	P Value
LADi quartile								
Q1 (LADi <2.40), n=363	43 (11.8)	5.2	1.00	Reference	0.93	1.00	Reference	0.84
Q2 (2.40 ≤ LADi <2.76), n=374	47 (12.6)	5.3	1.02	0.67 to 1.54	0.13	1.04	0.69 to 1.58	0.11
Q3 (2.76 ≤ LADi <3.19), n=371	64 (17.3)	8.0	1.36	0.91 to 2.02	0.009	1.38	0.93 to 2.06	0.003
Q4 (3.19 ≤ LADi), n=356	75 (21.1)	10.5	1.71	1.14 to 2.56	0.003	1.86	1.24 to 2.80	0.001
P for trend					0.003			0.001
LADi per 1 cm/m ²	229 (15.6)	7.9	1.48	1.19 to 1.84	<0.001	1.59	1.27 to 2.00	<0.001

Event rate was calculated as number of events per 100 patient-y. The multivariable model included age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases. The subdistribution hazard ratio was estimated by regarding death as a competing risk by the Fine-Gray model. HR indicates hazard ratio; LADi, left atrial diameter index; Q1 to Q4, quartiles of left atrial diameter index (cm/m²).

measurement of LAD, which is reproducible in the evaluation of left atrial size and has been widely used in clinical practice, is a useful marker to predict the future risk of recurrent stroke in NVAF patients. Thus, further study is required to elucidate the relationship between biomarkers and left atrial enlargement as a stroke risk in patients with atrial fibrillation.

This study has some limitations. There was a possibility of selection bias because 274 patients were excluded from the study because of the absence of data on LADi or follow-up (Figure S1). However, baseline characteristics did not differ between those with and without data on transthoracic echocardiography (Table S3). The measurement of LAD was not standardized because ultrasonographers at each institution performed the examination during hospitalization using the echocardiographic equipment available at each institution. Since left atrial dilatation can occur spatially in an asymmetric way, LAD does not always represent actual left atrial volume. Additionally, this study did not consider how patients were treated during the follow-up period. Although these real-world settings may weaken the association, they also suggest the

robustness of the findings. Finally, this study included only Japanese patients hospitalized in a defined geographic region, which limits the generalizability of our findings.

Conclusions

LADi was independently associated with the risk of recurrent stroke in NVAF patients with previous ischemic stroke. Patients with NVAF and large left atrium should be considered at high risk for future recurrent stroke.

Appendix

Participating Hospitals in the Fukuoka Stroke Registry

Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Nippon Steel Yawata Memorial Hospital,

Table 5. Added Predictive Ability of LADi for the Risk of Recurrent Stroke

	C-Index (95% CI)	IDI (95% CI)	Relative IDI (95% CI)	Continuous NRI (95% CI)
CHADS ₂ score				
Baseline model*	0.592 (0.542–0.632)			
Baseline model+LADi†	0.623 (0.586–0.665)	0.023 (0.017–0.028)	0.712 (0.527–0.839)	0.246 (0.052–0.386)
CHA ₂ DS ₂ -VaSc score				
Baseline model‡	0.591 (0.541–0.631)			
Baseline model+LADi§	0.625 (0.588–0.667)	0.021 (0.017–0.028)	0.623 (0.506–0.817)	0.231 (0.036–0.384)

C-index indicates concordance index; IDI, integrated discrimination improvement; LADi, left atrial diameter index; NRI, net reclassification improvement.

*The baseline model included the risk factors of the CHADS₂ score (ie, age, hypertension, chronic heart failure, and diabetes mellitus).

†LADi was additionally included in the baseline model composed of the factors included in the CHADS₂ score.

‡Baseline model included risk factors of the CHA₂DS₂-VASc score (ie, age, sex, hypertension, chronic heart failure, diabetes mellitus, and vascular diseases).

§LADi was additionally included in the baseline model composed of the factors of the CHA₂DS₂-VASc score.

and Japan Labour Health and Welfare Organization Kyushu Rosai Hospital.

Steering Committee and Research Working Group in the Fukuoka Stroke Registry

The steering committee of the Fukuoka Stroke Registry included Takao Ishitsuka (Fukuoka Mirai Hospital), Setsuro Ibayashi (Seiai Rehabilitation Hospital), Kenji Kusuda (Seiai Rehabilitation Hospital), Kenichiro Fujii (Japan Seafarers Relief Association Moji Ekisai Hospital), Tetsuhiko Nagao (Midorino Clinic), Yasushi Okada (National Hospital Organization Kyushu Medical Center), Masahiro Yasaka (National Hospital Organization Kyushu Medical Center), Hiroaki Ooboshi (Fukuoka Dental College Medical and Dental Hospital), Takanari Kitazono (Kyushu University), Katsumi Irie (Hakujyuji Hospital), Tsuyoshi Omae (Imazu Red Cross Hospital), Kazunori Toyoda (National Cerebral and Cardiovascular Center), Hiroshi Nakane (National Hospital Organization Fukuoka-Higashi Medical Center), Masahiro Kamouchi (Kyushu University), Hiroshi Sugimori (Saga-Ken Medical Centre Koseikan), Shuji Arakawa (Steel Memorial Yawata Hospital), Kenji Fukuda (St. Mary's Hospital), Tetsuro Ago (Kyushu University Hospital), Jiro Kitayama (Fukuoka Red Cross Hospital), Shigeru Fujimoto (Jichi Medical University), Shoji Arihiro (Japan Labor Health and Welfare Organization Kyushu Rosai Hospital), Junya Kuroda (Kyushu University Hospital), Yoshinobu Wakisaka (Kyushu University Hospital), Yoshihisa Fukushima (St. Mary's Hospital), and Ryu Matsuo (Kyushu University).

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Hazard ratios of secondary outcomes according to LADi

	Events (%)	Event rate per 100 patient-yr	Age- and sex-adjusted HR		Multivariable-adjusted HR	
			HR (95% CI)	P	HR (95% CI)	P
Death from any cause						
LADi quartile						
Q1 (LADi <2.40), n=405	96 (23.7)	9.6	1.00 (reference)		1.00 (reference)	
Q2 (2.40 ≤LADi <2.76), n=405	105 (25.9)	10.3	1.11 (0.84-1.46)	0.48	1.10 (0.83-1.46)	0.51
Q3 (2.76 ≤LADi <3.19), n=401	146 (36.4)	15.9	1.29 (0.99-1.68)	0.06	1.29 (0.99-1.68)	0.06
Q4 (3.19 ≤LADi), n=400	167 (41.8)	18.3	1.30 (0.99-1.71)	0.06	1.28 (0.97-1.69)	0.08
P for trend				0.04		0.05
LADi per 1 cm/m ²	514 (31.9)	13.3	1.23 (1.06-1.43)	0.006	1.22 (1.05-1.41)	0.01
Ischemic stroke						
LADi quartile						
Q1 (LADi <2.40), n=405	36 (8.9)	3.8	1.00 (reference)		1.00 (reference)	
Q2 (2.40 ≤LADi <2.76), n=405	43 (10.6)	4.5	1.15 (0.74-1.80)	0.53	1.17 (0.75-1.83)	0.49
Q3 (2.76 ≤LADi <3.19), n=401	57 (14.2)	6.6	1.47 (0.96-2.27)	0.08	1.49 (0.97-2.29)	0.07
Q4 (3.19 ≤LADi), n=400	83 (20.8)	10.5	2.20 (1.44-3.37)	<0.001	2.35 (1.54-3.60)	<0.001
P for trend				<0.001		<0.001
LADi per 1 cm/m ²	219 (13.6)	6.1	1.62 (1.31-2.01)	<0.001	1.71 (1.37-2.13)	<0.001
Hemorrhagic stroke						
LADi quartile						
Q1 (LADi <2.40), n=405	11 (2.7)	1.1	1.00 (reference)		1.00 (reference)	
Q2 (2.40 ≤LADi <2.76), n=405	8 (2.0)	0.8	0.74 (0.30-1.84)	0.51	0.79 (0.31-1.97)	0.61
Q3 (2.76 ≤LADi <3.19), n=401	12 (3.0)	1.3	1.22 (0.52-2.87)	0.65	1.30 (0.55-3.05)	0.55
Q4 (3.19 ≤LADi), n=400	3 (0.8)	0.3	0.32 (0.08-1.23)	0.10	0.37 (0.10-1.40)	0.14
P for trend				0.30		0.42
LADi per 1 cm/m ²	34 (2.1)	0.9	0.72 (0.38-1.40)	0.33	0.79 (0.41-1.53)	0.48

LADi: left atrial diameter index, HR: hazard ratio, CI: confidential interval. Q1 to Q4 indicate quartiles of left atrial diameter index (cm/m²). Stroke included ischemic and hemorrhagic stroke. The event rate was calculated as number of events per 100 patient-years. The multivariable model included age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases.

Table S2. Coagulation status at index stroke according to LADi

	Q1, n=405 LADi <2.40	Q2, n=405 2.40 ≤LADi <2.76	Q3, n=401 2.76 ≤LADi <3.19	Q4, n=400 3.19 ≤LADi	P for trend
Pre-stroke anticoagulation therapy, n (%) [*]	101 (24.9) [n=0]	115 (28.4) [n=0]	138 (34.4) [n=0]	168 (42.0) [n=0]	<0.001
PT-INR on admission, mean±SD [†]	1.45±0.43 [n=1]	1.47±0.53 [n=0]	1.62±0.49 [n=0]	1.55±0.48 [n=2]	0.02
D-dimer on admission, µg/mL, mean±SD [‡]	2.47±4.90 [n=56]	2.68±6.64 [n=67]	2.86±5.41 [n=60]	3.61±6.15 [n=71]	<0.001
Spontaneous echo contrast, n (%) [§]	15 (17.2) [n=318]	27 (24.1) [n=293]	33 (44.6) [n=327]	34 (49.3) [n=331]	<0.001
PT-INR at discharge, mean±SD [†]	2.10±0.59 [n=0]	2.16±0.64 [n=0]	2.13±0.57 [n=0]	2.19±0.61 [n=0]	0.11

LADi: left atrial diameter index, SD: standard deviation; PT-INR: prothrombin time-international normalized ratio. Q1 to Q4 indicate quartiles of left atrial diameter index (cm/m²). The number in brackets ([n]) indicates the number of missing values. ^{*}Pre-stroke anticoagulation therapy was defined as oral anticoagulants prescribed before onset. Oral anticoagulants included warfarin and direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban). [†]PT-INR was measured in patients who were treated with warfarin. [‡]D-dimer was measured on admission. [§]Transesophageal echocardiography was performed during hospitalization for the index stroke.

Table S3. Baseline characteristics of patients included and excluded because of lack of data on LADi

	Included n=1784	Excluded n=240	P
Age, yr, mean±SD	78.0±10.1	79.2±10.1	0.07
Female, n (%)	797 (87.7)	112 (12.3)	0.56
Risk factors, n (%)			
Hypertension	1389 (77.9)	180 (78.8)	0.75
Diabetes mellitus	422 (23.7)	67 (27.9)	0.15
Vascular diseases	408 (22.9)	61 (25.4)	0.38
Ischemic heart disease	339 (19.0)	53 (22.1)	0.26
Peripheral arterial disease	112 (6.3)	15 (6.3)	0.99
Chronic heart failure	340 (19.1)	49 (20.4)	0.62

LADi: left atrial diameter index, SD: standard deviation

Figure S1. Flow chart of patient selection

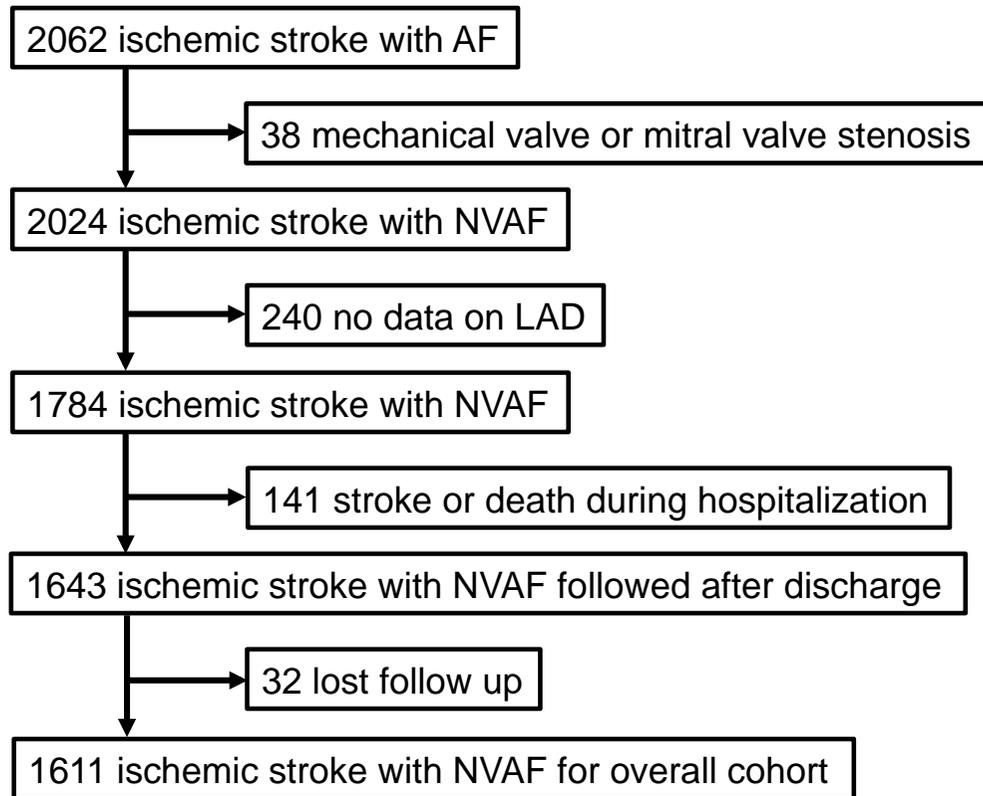
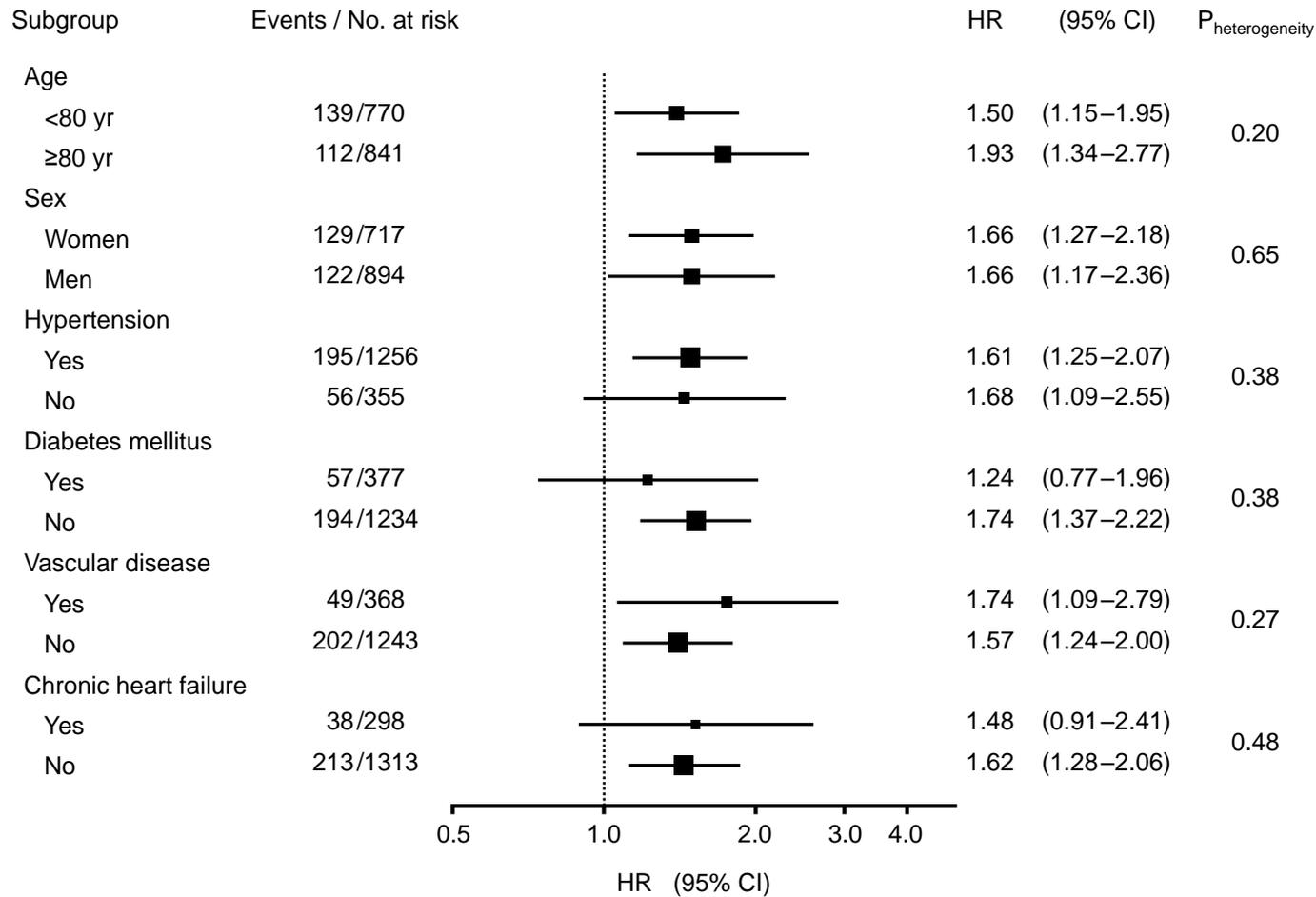


Figure S2. Hazard ratios of recurrent stroke in subgroups

Hazard ratios of recurrent stroke were estimated in each subgroup. The multivariable model included age, sex, hypertension, diabetes mellitus, chronic heart failure, and vascular diseases. P for heterogeneity ($P_{\text{heterogeneity}}$) was tested by interaction term.

Left Atrial Size and Long-Term Risk of Recurrent Stroke After Acute Ischemic Stroke in Patients With Nonvalvular Atrial Fibrillation

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