

Japanese and Non-Japanese Patients with Transient Ischemic Attack or Minor Stroke: A Five-Year Risk Analysis of Stroke and Vascular Events

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Aims: We have previously reported 5-year follow-up data on the TIAregistry.org, an international prospective cohort in patients with transient ischemic attack (TIA) or minor stroke. We conducted a Japanese subgroup analysis because outcomes and predictors might differ according to ethnicities and regions. In this study, we compared the baseline and 5-year follow-up data of Japanese and non-Japanese patients with TIA or minor stroke.

Methods: Patients with TIA or minor ischemic stroke within 7 days after the onset were classified into two groups based on ethnicity, Japanese ($n=345$) and non-Japanese ($n=3502$); further, 5-year event rates were compared between the two groups. We also determined predictors of 5-year stroke for both groups.

Results: Vascular death and death from any cause were identified to be less prevalent, unlike stroke and intracranial hemorrhage, which was determined to be more prevalent in Japanese than in non-Japanese patients. Five-year rate of stroke was significantly higher in Japanese patients. Cumulative stroke and major cardiovascular event rates did not decline but instead linearly increased from 1 to 5 years in both groups. Baseline risk factors for 5-year stroke were as follows: age, diabetes, history of stroke or TIA, and congestive heart failure in Japanese patients. Independent predictors of 5-year stroke were large artery atherosclerosis, congestive heart failure, diabetes, and age in Japanese patients.

Conclusions: Recurrent stroke and intracranial hemorrhage were determined to be more prevalent at 5 years after TIA or minor stroke in Japanese patients than in non-Japanese patients. Strategies to mitigate the long-term risks of stroke, aside from adherence to current guidelines, should take Japanese-patient-specific residual risks into account.

Key words: Transient ischemic attack, Stroke, Risk factor, Predictor, Outcome

Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Factor for Occluded Coronary Arteries; TOAST, Trial of Org 10172 in Acute Stroke Treatment

Introduction

The TIAregistry.org is an international, multi-center-cooperative, prospective registry of transient ischemic attack (TIA) or minor ischemic stroke within 7 days after the onset¹. In a previous Japanese subgroup analysis using the 1-year follow-up data of the TIAregistry.org, differences in risk factors, stroke subtypes, and outcome events were determined between Japanese and non-Japanese patients, and the predictors for recurrent stroke among Japanese patients included congestive heart failure (CHF) and regular alcohol drinking². However, the results were preliminary as the follow-up period was only 1 year. Thereafter, we reported the results of our analysis using the 5-year follow-up data in this registry and further showed a sustained risk of cardiovascular events over a period of 5 years³.

Aim

We have conducted a Japanese subgroup analysis on the 5-year follow-up data obtained from the TIAregistry.org in order to compare the long-term outcomes and predictors between Japanese and non-Japanese patients with TIA or minor ischemic stroke.

Methods

Study Design

The methods used for patient recruitment and evaluation for the TIAregistry.org project have been described previously¹. The protocol has been approved by the local institutional review boards. All patients provided written or oral informed consent as per country regulation. Sites in the registry from 21 countries have been described previously¹. Sites with follow-up data on >50% of their enrolled patients at 5 years were included for the analysis in this report. These sites were identified to be academic centers distributed among Europe, Asia, and Latin America. Data collection has also been reported previously¹. They were collected prospectively using a Web-based case-report form at the time of evaluation of the qualifying event at baseline, 1, 3, and 12 months and every 12 months for 5 years.

Events and Outcomes

Primary outcome was a composite of death from cardiovascular causes, nonfatal stroke (ischemic or

hemorrhagic), or nonfatal acute coronary syndrome. Definitions of primary outcome events have already been described¹. Secondary outcomes included individual components of the primary outcome, TIA recurrence, death from any cause, any bleeding, and the modified Rankin Scale (mRS) at last follow-up. TIA has been defined as new neurologic symptoms or deficits lasting <24 hours without new infarctions on neuroimaging. Bleeding was then categorized as severe or life-threatening, moderate, or mild as per the GUSTO definitions. Primary outcome and all bleeding events were adjudicated by two investigators according to the clinical records.

Statistical Analysis

Quantitative variables were expressed as means (\pm standard deviation) in case of normal distribution or median (interquartile range) if otherwise. Meanwhile, categorical variables were expressed as numbers (percentage). Shapiro-Wilk test was utilized to graphically assess the normality of distributions. Baseline characteristics and medication use at discharge and at 1 and 5 years were compared between Japanese and non-Japanese patients. All comparisons between the two groups were adjusted for age and sex by using the analysis of covariance for quantitative variables, logistic regression models for binary variables, and multinomial regression models for categorical variables.

The 5-year event rates were then compared between the two groups using the Cox proportional-hazards regression model, which was adjusted for age, sex, mRS, and ABCD² score. Non-Japanese patients were used as a reference in calculating the hazard ratios as effect size measures, with 95% confidence interval. Cumulative event curves were constructed using the Kaplan–Meier method.

The ABCD² score, acute infarctions identified on brain imaging, and probable causes of initial TIA or minor stroke according to the TOAST classification have been tested with stroke recurrence using Cox proportional-hazards model in the two groups separately. The proportional-hazards assumption was verified using the Schoenfeld residuals.

We then identified the independent predictors of 5-year stroke by first establishing age-, sex- and mRS-adjusted Cox proportional-hazards regression models in Japanese and non-Japanese patients separately. Candidate predictors were as follows: demographic characteristics, medical history, mRS, and major investigational findings. We then performed region-specific

Table 1. Background characteristics at baseline

	Japanese <i>n</i> = 345	Non-Japanese <i>n</i> = 3502	<i>P</i> -value
Age, mean (SD), year	68.1 (11.2)	66.3 (13.4)	0.005
Male sex	244/345 (70.7%)	2051/3496 (58.7%)	<0.001
Hypertension	224/345 (64.9%)	2483/3492 (71.1%)	<0.001
Diabetes	73/345 (21.2%)	654/3487 (18.8%)	0.51
Dyslipidemia	177/345 (51.3%)	2532/3502 (72.3%)	<0.001
Current smoker	92/345 (26.7%)	743/3456 (21.5%)	0.005
Regular alcohol consumption	133/345 (38.6%)	66/3456 (19.2%)	<0.001
Physical activity [§]	88/345 (25.7%)	713/3369 (21.2%)	0.045
Atrial fibrillation	39/345 (9.0%)	395/3491 (8.5%)	0.12
History of stroke or transient ischemic attack	90/345 (26.1%)	568/3502 (16.2%)	<0.001
Coronary artery disease	30/344 (8.7%)	451/3489 (12.9%)	0.005
Peripheral artery disease	9/345 (2.6%)	104/3474 (3.0%)	0.53
Congestive heart failure	8/345 (2.3%)	101/3491 (2.9%)	0.55

[§]Physical activity was defined as any activity performed during at least 4 hours or more per week.

stepwise-backward multivariable Cox proportional-hazards regression analysis by including all candidate predictors associated with outcomes at age-, sex- and mRS-adjusted *p*-value <0.10. Age and sex were integrated into the model, and the removal criterion (*p*-value from the Wald test) of 0.05 was utilized. Before multivariable prognostic models are developed, we first examined the proportional-hazards assumptions for each candidate predictor using the Schoenfeld residuals plots, log-linearity assumption for continuous candidate predictors using the Martingale residual plots, and absence of co-linearity between candidate predictors by calculating the variance inflation factors. Estimates obtained from the different imputed data sets were integrated using Rubin's rules. The predictive ability of the models was then calculated in Japanese and non-Japanese patients by using Harrell's C-statistic.

Statistical testing was performed at a two-tailed α level of 0.05. Data were analyzed using SAS software package, release 9.3 (SAS Institute, Cary, NC).

Results

Background Characteristics

Patients with TIA or minor ischemic stroke within 7 days after the onset were classified into two groups based on ethnicity, Japanese (*n*=345) and non-Japanese (*n*=3502). Non-Japanese patients included were as follows: 537 Asian patients (China, *n*=347; Korea, *n*=99; Taiwan, *n*=66; and Lebanon, *n*=25) and 2965 non-Asian patients (Germany, *n*=641; France, *n*=640; Spain, *n*=555; Czech, *n*=516; UK, *n*=213; Portugal, *n*=181; Italy, *n*=117; Ireland,

n=72; and Mexico, *n*=30). The Japanese patients were older, and more frequently are males, current cigarette smokers, regular alcohol drinkers, and with a history of stroke or TIA, but they had less hypertension, dyslipidemia, and coronary artery disease compared to non-Japanese patients (Table 1). In Japanese patients, ABCD² scores 1–3 were found to be less common, but ABCD² scores 6 and 7 were more common (Table 2). Regarding TOAST classification, small vessel occlusion was more common, but undetermined etiology was less common in Japanese patients (Table 2). Regarding brain and vascular imaging, Japanese patients frequently had acute infarctions and intracranial arterial stenoses but less frequently had extracranial arterial stenoses (Table 2).

Medication Use

In Japanese patients, the use of antiplatelet agents was less common after 1 year, while the use of anticoagulants with and without antiplatelet agents, which was more common after 1 year and at 5 years (Table 3). Further, the use of lipid-lowering agents was less common after 1 year and at 5 years unlike glucose-lowering agents, which were commonly used after 5 years in Japanese patients (Table 3).

Five-Year Event Rate

Vascular death, death from any cause, and TIA were identified to be less prevalent, whereas nonfatal stroke and intracranial hemorrhage were more prevalent in Japanese patients than in non-Japanese patients (Table 4). Kaplan–Meier curves at 5 years showed non-significantly higher major cardiovascular event rates (Fig. 1) and significantly higher stroke rates in

Table 2. Baseline ABCD² score, TOAST classification, and brain and vascular imaging

	Japanese <i>n</i> = 345	Non-Japanese <i>n</i> = 3502	<i>P</i> -value*
ABCD ² score			< 0.001
0-3	65/315 (20.6%)	1038/3101 (33.5%)	
4-5	161/316 (50.9%)	1480/3101 (47.7%)	
6-7	90/316 (28.5%)	583/3101 (18.8%)	
TOAST classification			< 0.001
Large artery atherosclerosis	86/345 (24.9%)	790/3213 (24.6%)	
Small vessel occlusion	133/345 (38.6%)	630/3213 (19.2%)	
Cardioembolism	56/345 (16.2%)	506/3213 (15.7%)	
Other determined causes	26/345 (7.6%)	170/3213 (5.3%)	
Undetermined	45/345 (13.0%)	1117/3213 (34.8%)	
Infarct on CT or MRI	270/345 (78.3%)	1460/3349 (43.6%)	< 0.001
Extracranial stenosis > 50%	37/318 (11.6%)	513/3183 (16.1%)	0.010
Intracranial stenosis > 50%	67/341 (19.7%)	381/2874 (13.3%)	0.007

*Adjusted by age and sex

Table 3. Medication use at 1 and 5 years

Medication	At 1 year		At 5 years	
	Japanese (<i>n</i> = 340)	Non-Japanese (<i>n</i> = 3225)	Japanese (<i>n</i> = 302)	Non-Japanese (<i>n</i> = 2647)
Antiplatelet therapy	249/336 (74.1%)*	2493/3102 (80.4%)	199/277 (71.8%)	1724/2353 (73.3%)
Anticoagulant therapy	90/337 (26.7%)**	511/3087 (16.6%)	75/277 (27.1%)**	386/2355 (16.4%)
Antiplatelet and anticoagulant therapies	21/340 (6.2%)**	75/3187 (2.4%)	17/302 (5.6%)**	45/2406 (1.9%)
Lipid-lowering therapy	178/337 (52.8%)**	2184/3068 (71.2%)	162/277 (58.5%)*	1566/2356 (66.5%)
Glucose-lowering therapy	66/336 (19.6%)	520/3055 (17.0%)	66/277 (23.8%)*	413/2353 (14.6%)

Shown are cumulative frequencies at different time points.

*Age- and sex-adjusted $p < 0.05$ **Age- and sex-adjusted $p < 0.0005$ **Table 4.** Primary and secondary outcomes

	Japanese <i>n</i> = 345	Non-Japanese <i>n</i> = 3502	HR (95% CI)	<i>P</i> -value
Primary outcome				
Major CV events	55 (16.6%)	414 (12.9%)	1.01 (0.75-1.38)	0.93
Vascular death	3 (0.9%)	93 (3.0%)	0.031 (0.16-0.64)	0.01
Nonfatal stroke	48 (14.4%)	253 (7.9%)	1.54 (1.10-2.15)	0.013
Nonfatal ACS	6 (1.9%)	73 (2.4%)	0.56 (0.22-1.40)	0.21
Secondary outcome				
Any death	27 (8.1%)	346 (10.9%)	0.60 (0.40-0.91)	0.016
Stroke	49 (14.7%)	296 (9.2%)	1.28 (0.92-1.78)	0.15
TIA	11 (3.3%)	296 (9.0%)	0.45 (0.25-0.84)	0.011
Intracranial hemorrhage	11 (3.4%)	28 (0.9%)	2.52 (1.09-5.81)	0.030
Major bleeding	12 (3.8%)	41 (1.4%)	1.97 (0.92-4.24)	0.083

Data adjusted by age, sex, modified Rankin Scale score, and ABCD² score.

Abbreviations: HR; hazard ratio, CI; confidence interval, CV; cardiovascular, ACS; acute coronary syndrome, TIA; transient ischemic attack

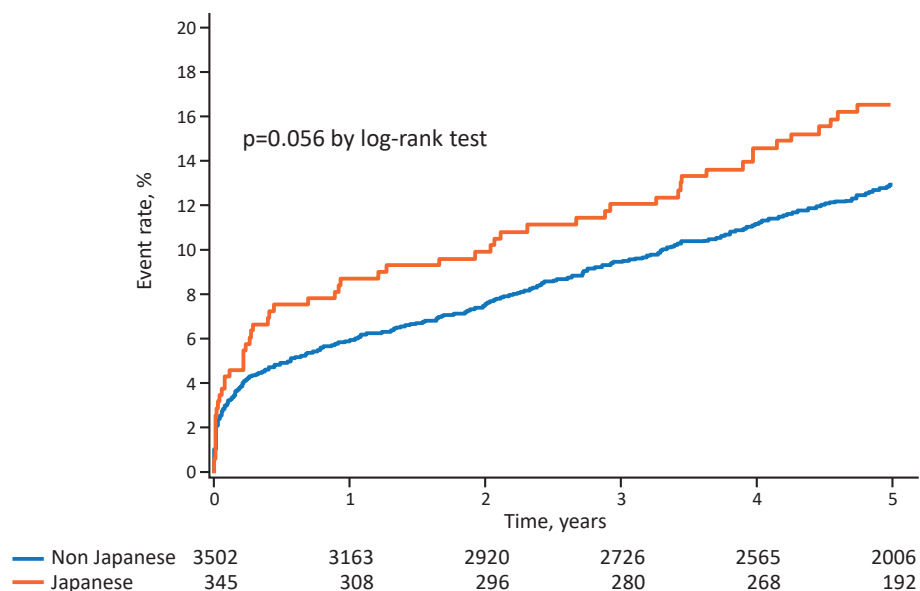


Fig. 1. Kaplan–Meier curves of major cardiovascular events

The rate of major cardiovascular events was non-significantly higher in Japanese patients. Cumulative stroke rate curves did not decline but linearly increased in parallel during the second to fifth year in both Japanese and non-Japanese patients.

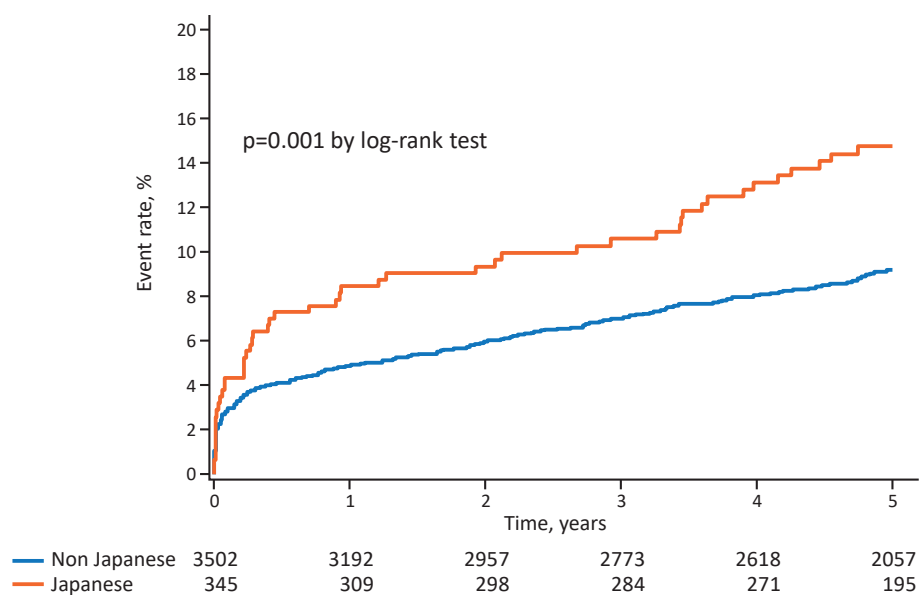


Fig. 2. Kaplan–Meier curves of recurrent stroke

The stroke rate was significantly higher in Japanese patients. Cumulative stroke rate curves did not decline but linearly increased in parallel during the second to fifth year in both Japanese and non-Japanese patients.

Japanese patients (**Fig. 2**). Recurrent stroke rates were 8.4% and 4.8% at 1 year and 14.7% and 9.2% at 5 years in Japanese and non-Japanese patients, respectively.

Risk Factors and Predictors for 5-Year Stroke

Large artery atherosclerosis (LAA) was a predic-

tor of recurrent stroke after 5 years in a subgroup analysis, according to the TOAST classification at baseline (**Fig. 3**). Age, diabetes, history of stroke or TIA, coronary artery disease, and CHF at baseline were risk factors of recurrent stroke after 5 years among Japanese patients (**Table 5**). The Cox proportional-hazards regression model demonstrated that

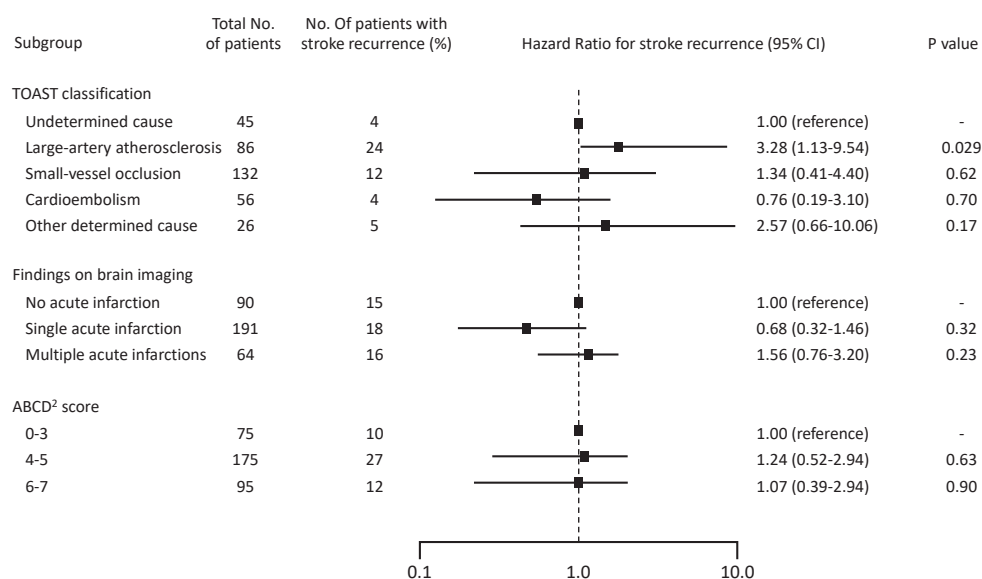


Fig. 3. Multivariate subgroup analysis of the predictors for stroke recurrence according to the Trial of Org 10172 in Acute Stroke Treatment classification, findings on brain imaging, and ABCD² score at baseline for recurrent stroke at 5 years among Japanese patients.

Table 5. Risk of 5-year stroke by baseline characteristics

	Japanese		Non-Japanese	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (per 10 years)	1.35 (1.02-1.79)	0.039	1.25 (1.13-1.37)	<0.001
Men	1.40 (0.73-2.69)	0.31	1.32 (1.04-1.69)	0.024
Hypertension	1.58 (0.82-3.03)	0.17	1.24 (0.92-1.67)	0.16
Diabetes	2.03 (1.13-3.66)	0.018	1.56 (1.20-2.03)	<0.001
Dyslipidemia	1.14 (0.65-1.99)	0.66	0.97 (0.74-1.28)	0.83
Current smoker	1.51 (0.74-3.07)	0.25	1.15 (0.83-1.59)	0.40
Regular alcohol consumption	1.60 (0.91-2.81)	0.10	0.96 (0.71-1.29)	0.78
History of stroke or TIA	1.86 (1.05-3.30)	0.035	1.69 (1.29-2.20)	<0.001
Coronary artery disease	2.15 (1.01-4.59)	0.049	1.19 (0.86-1.63)	0.29
Peripheral artery disease	1.06 (0.15-7.68)	0.95	1.33 (0.74-2.37)	0.34
Congestive heart failure	4.54 (1.63-12.64)	0.004	1.46 (0.83-2.57)	0.19

Data adjusted by age, sex, and modified Rankin Scale score.

CHF, diabetes, and age were independent predictors for recurrent stroke after 5 years (Table 6).

Discussion

Differences in the baseline risk factors between Japanese and non-Japanese patients in this study were determined to be similar to those obtained in the 1-year follow-up analysis reported previously, since 80 % of the patients in the 1-year follow-up study were selected in this study^{1, 3}. The higher proportions of AIS and high-risk TIA in Japanese patients suggest that we have recruited exclusively admitted patients

with AIS and high-risk TIA⁴ but not recruited lower-risk TIA because of few TIA clinics in Japan².

The use of antiplatelet drugs was less common unlike anticoagulants, which were determined to be commonly used among Japanese patients. Using antiplatelet drugs has declined during the 1- to 5-year follow-up among both Japanese and non-Japanese patients. Discontinuation of antiplatelet therapy may increase the risk of stroke recurrence⁵. Prescription rate of anticoagulants was found to be higher than the rates of atrial fibrillation and cardioembolism at baseline among Japanese patients, suggesting that anticoagulants were used in patients with other determined

Table 6. Independent predictors for 5-year stroke in Japanese and non-Japanese patients

	HR (95% CI)	<i>P</i> -value
Japanese		
Congestive heart failure	4.43 (1.55-12.66)	0.006
Diabetes	2.31 (1.26-4.24)	0.007
Age (per 10 years)	1.38 (1.03-1.85)	0.031
Non-Japanese		
Diabetes	1.48 (1.14-1.92)	0.003
Age (per 10 years)	1.16 (1.05-1.28)	0.003
Single acute infarct	1.39 (1.05-1.85)	0.022
Multiple acute infarct	1.73 (1.28-2.35)	<0.001
Extracranial stenosis >50%	1.60 (1.21-2.13)	0.001
Cardioembolism	1.59 (1.10-2.30)	0.013

Cox proportional hazard regression model was used for analysis.

The Haller C index for stroke recurrence was 0.69 (95% CI: 0.61-0.77) and 0.68 (95% CI: 0.65-0.71) for Japanese and non-Japanese patients, respectively.

or undetermined causes as well⁶.

Nonfatal stroke rate was found to be higher in Japanese patients. The higher rate of stroke recurrence might be attributed to the higher stroke risk among Japanese patients than among non-Japanese patients selected in this study, because there were more Japanese patients with AIS and high-risk TIA as well as history of stroke or TIA. Nevertheless, vascular death was less common in Japanese patients. In the 1-year follow-up study, the comparison between the two groups was not performed because of the small number of events². These results indicate that fatal stroke and fatal MI were found to be fewer in Japanese patients.

Intracranial hemorrhage was more common among Japanese patients. In the 1-year follow-up data, comparison in intracranial hemorrhage between the two groups was not applicable because of small number of events. We confirmed that intracranial hemorrhage was more prevalent in Japanese patients than in non-Japanese patients in this 5-year follow-up study. It has been suggested that the Japanese population is more at risk for intracranial hemorrhage compared with the Western population^{7, 8}. Regarding ethnicities, in the Asian (Japan, China, Korea, Taiwan, Thailand, and Malaysia) and non-Asian (Europe and Latin America) patients compared in the TIAregistry.org 5-year follow-up study, the risk of intracranial hemorrhage was also higher in Asian patients (under article submission). Therefore, the high risk of intracranial hemorrhage is a characteristic of both Japanese and other Asian patients. Anticoagulants with and without antiplatelet agents were more frequently used in Japanese patients, despite the fact that the risk of hemorrhage is deemed higher with anticoagulants and much

higher with combination of anticoagulants and antiplatelet drugs than with antiplatelet drugs alone⁹. Therefore, the risk-benefit of antithrombotics should be carefully balanced in Japanese patients¹⁰.

The rate of major cardiovascular events was non-significantly higher, and the stroke rate was significantly higher in Japanese patients. This may be explained mainly by the higher risk of Japanese patients selected in this study². Cumulative stroke rate curves did not decline but instead linearly increased in parallel during the second to fifth year in both Japanese and non-Japanese patients³. The risk factors for 5-year stroke at baseline were age, diabetes, history of stroke or TIA, and CHF, whereas the independent predictors for 5-year stroke were age, LAA, CHF, and diabetes in Japanese patients. LAA, CHF, and diabetes were also identified predictors for 1-year stroke in Japanese patients².

In the TIAregistry.org, the 1-year stroke risk by TOAST classification was significantly high both in Japanese and non-Japanese patients with LAA². In this 5-year follow-up study, LAA was again an independent predictor for stroke recurrence at 5 years in Japanese patients. In the comparison between Asian and non-Asian patients in the TIAregistry.org 5-year follow-up study, although an analysis according to the TOAST classification was not performed, intracranial arterial stenosis was also determined as an independent predictor of the primary outcome in Asian patients (under article submission). LAA is a poly-vascular disease, which includes atherothrombotic stroke, TIA, coronary artery disease, and peripheral artery disease, and the risk of vascular events in patients with LAA increases as the number of involved vascular beds increases¹¹. Therefore, to reduce the residual risk of

composite vascular events in patients with LAA, more intensive antiplatelet therapy and total risk management are needed^{12, 13}).

In our previous 1-year follow-up study, CHF was the strongest predictor for stroke recurrence in Japanese patients³). In this 5-year follow-up study, CHF was again the strongest predictor for 5-year stroke in Japanese patients. It is well known that CHF is a risk factor for stroke in patients with atrial fibrillation, although CHF can cause stroke without atrial fibrillation and, therefore, should be considered as an independent risk factor for stroke¹⁴). The mechanism of stroke in CHF patients is primarily embolic, and the risk of stroke is associated with left ventricular dysfunction and dilatation¹⁴). The number of patients with CHF is increasing along with the increase of the elderly population^{15, 16}). The higher mean age of Japanese patients may contribute to the increased risk of recurrent stroke induced by heart failure^{17, 18}).

In our previous 1-year follow-up study, diabetes was a non-significant predictor for stroke recurrence in Japanese patients²). In this 5-year follow-up study, diabetes was identified as a significant predictor for stroke recurrence. The number of patients with diabetes has remarkably increased due to the Westernization of diet and increasing number of elderly subjects in Japan^{19, 20}). Therefore, diabetes as a risk factor for stroke is becoming more important, but the management of diabetes for stroke prevention is still insufficient²¹). The J-DOIT 3 trial showed that multiple aggressive interventions dramatically reduced the stroke risk compared with conventional treatments in Japanese diabetic patients²²). The results of J-DOIT 3 suggest that more intensive total risk management in addition to the current guidelines can reduce the residual risk of recurrent stroke also in patients with TIA and minor stroke.

There are limitations in this study. First, owing to its observational nature, even after extensive adjustment, residual confounding cannot be ruled out. Second, because the participating sites were not selected randomly, the cohort analyzed in this study could differ from the general TIA/stroke population. Third, the relatively small sample of Japanese patients may have caused type II errors in our statistical analysis, which may negatively affect our findings on the risk factors and predictors.

Conclusion

Recurrences of stroke and intracranial hemorrhage at 1 and 5 years after TIA or minor stroke were determined to be more frequent in Japanese patients than in non-Japanese patients. Predictors for stroke

recurrence were identified as follows: LAA, CHF, and diabetes in Japanese patients with acute cerebrovascular syndrome. Strategies to reduce the long-term risk of stroke, aside from adherence to the current guidelines, should take Japanese-patient-specific residual risks into account. Our Japanese-specific data would contribute to the development of long-term stroke prevention strategies specifically tailored to Japanese patients with TIA or minor stroke as well as projects for the appropriate allocation of resources for their care.

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Conflicts of Interest Statement

The authors declare that there is no conflict of interest.

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