

# Japanese Versus Non-Japanese Patients with Transient Ischemic Attack or Minor Stroke: Subanalysis of TIA registry.org

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**Background:** TIAregistry.org is an international cohort of patients with transient ischemic attack (TIA) or minor stroke within 7 days before enrollment in the registry. Main analyses of 1-year follow-up data have been reported.<sup>5</sup> We conducted subanalysis on the baseline and 1-year follow-up data of Japanese patients. **Methods:** The patients were classified into 2 groups based on Japanese ethnicity, Japanese (345) and non-Japanese (3238), and their baseline data and 1-year event rates were compared. We also determined risk factors and predictors of 1-year stroke. **Results:** Current smoking, regular alcohol drinking, intracranial arterial stenosis, and small vessel occlusion; and hypertension, dyslipidemia, coronary artery disease, and extracranial arterial stenosis were more and less common among Japanese patients, respectively. Stroke risk was higher and TIA risk was lower at 1-year follow-up among Japanese patients. The baseline risk factors for recurrent stroke were diabetes, alcohol drinking, and large artery atherosclerosis. Independent predictors of 1-year stroke risk were prior congestive heart failure and alcohol consumption. **Conclusions:** The two populations of patients featured differences in risk factors, stroke subtypes, and outcome events. Predictors of recurrent stroke among Japanese patients included congestive heart failure and regular alcohol drinking. Strategies to attenuate residual risk of stroke aside from adherence to current guidelines should take our Japanese-patient specific findings into account. **Key Words:** Transient ischemic attack—stroke—risk factor—predictor—outcome.

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## Introduction

Though transient ischemic attack (TIA) is a well-known prodromal syndrome of ischemic stroke, it is easily disregarded by patients and their families because its symptoms dissipate without treatment. Even by general physicians, TIA is considered to be a minor stroke and is consequently nonprioritized.<sup>1,2</sup> However, the risk of more severe stroke during the period immediately following the incidence TIA is very high.<sup>3</sup> TIA should therefore be recognized as a medical emergency requiring immediate evaluation and treatment.<sup>4</sup> The duration of TIA with acute ischemic lesions features a continuous distribution lacking a specific cut-off point.<sup>1</sup> TIA is thus undifferentiable from ischemic stroke by the duration of the symptoms. Therefore, TIA in acute setting and acute ischemic stroke (AIS) are on the same spectrum of acute ischemic syndrome in the central nervous system.

TIAREGISTRY.ORG was an international multicenter-cooperative, investigator-driven, observational study. We proposed the adoption of a new concept termed acute cerebrovascular syndrome (ACVS), which includes TIA in acute setting and AIS;<sup>1,2</sup> grouping the two conditions together promotes the recognition of TIA in acute setting as a medical emergency equivalent to AIS. We have previously published the main results of 1-year follow-up data analyses of TIAREGISTRY.ORG:<sup>5</sup> urgent intervention by stroke specialists in dedicated units by the recognition of TIA as an ACVS contributed to substantially reduce the risk of subsequent stroke and other cardiovascular events during recent 10 years. However, our results also indicated the need to further explore how the residual risk of stroke might be reduced aside from stricter adherence to the current optimal treatment guidelines.

We subsequently performed an Asian subanalysis of TIAREGISTRY.ORG because we suspected that the relevance of the following risk factors for stroke might differ according to race or ethnicity: stroke subtypes, genetic background, diet, lifestyle, socioeconomic status, and stroke care system.<sup>6</sup> Results of this subanalysis demonstrated that substantial racial or regional differences exist among various clinical and investigational parameters, as well as their impacts on the risk of stroke. We further speculated that these differences might also exist between Japanese and non-Japanese Asian patients. We therefore conducted a Japanese subanalysis of TIAREGISTRY.ORG. Specifically, we compared the baseline and 1-year follow-up data of Japanese and non-Japanese patients with TIA or minor stroke within 7 days before enrollment in the registry in the context of contemporary care systems. Additionally, we compared Japanese with non-Japanese Asian patients to identify characteristics specific to Japanese patients. Such Japan-specific data would help to inform stroke prevention strategies tailored to Japanese TIA patients as well as plans for the appropriate allocation of resources for their care.

## Materials and Methods

### *Study Design*

The design and primary results of the TIAREGISTRY.ORG have been reported elsewhere.<sup>5</sup> Briefly, the TIAREGISTRY.ORG was an investigator-driven, international, multicenter-cooperative, web-based, prospective, observational registry. The protocol was approved by local institutional review boards. The selected facilities were based in 21 countries; each featured a dedicated TIA/stroke patient-care system staffed by stroke specialists and received an annual volume of at least 100 patients during the previous 3 years prior to the study. The acute care setting included emergency departments, stroke units, day clinics, and outpatient clinics.

### *Subjects*

Eligible patients had focal brain ischemia with a resolution of symptoms within 24 hours of onset or a minor ischemic stroke with a modified Rankin scale (mRS) of 0 or 1 when first evaluated by a stroke specialist. A total of 4789 patients with TIA or minor stroke within 7 days of onset were enrolled between June 2009 and December 2011. All study patients provided informed consent. Patients were classified based on Japanese descent and are referred to throughout the manuscript as the following: Japanese and non-Japanese.

### *Data Collection*

Stroke specialists prospectively collected patient data with a standardized web-based case report form at the time of evaluation of the qualifying event (baseline), and at 1, 3, and 12 months following baseline; though the original dataset features additional evaluations every 12 months thereafter for 5 years, the present study analyzed data up to the 12-month evaluation. The baseline data included clinical symptoms, medical history, living and socioeconomic data, physical examination, lab tests including standard blood chemistry, brain and artery imaging, cardiac workup, and clinical management (medical treatment and revascularization procedure). An etiologic subtype of ischemic stroke was assigned according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.<sup>7</sup>

### *Outcome*

The primary outcome was defined as a composite of cardiovascular death, nonfatal stroke (ischemic or hemorrhagic), and nonfatal acute coronary syndrome (with or without ST elevation). The secondary outcomes included individual components of the primary outcome, TIA occurrence, all-cause mortality, and bleeding. Our definition of bleeding was informed by the Global Use of Strategies to Open Occluded Arteries (GUSTO).<sup>8</sup>

### Statistical Analysis

Quantitative variables were expressed as means  $\pm$  standard deviation in the case of normal distributions; otherwise, we used medians and interquartile ranges. Qualitative variables were expressed as counts (percentage). Normality of distributions was assessed graphically and by using the Shapiro-Wilk test. All comparisons between the 2 groups were adjusted for age, sex, and mRS. We used analysis of covariance for qualitative variables and logistic regression models for binary variables. For variables with skewed distributions, we performed linear regression analyses with log-transformed values.

Cumulative event curves were constructed using the Kaplan-Meier method. We compared the 1-year event rates (primary and secondary endpoint) between the 2 groups using Cox proportional hazard models adjusted for age, sex, and mRS. Adjusted event rates were calculated using the corrected group-prognosis method, while adjustments for age were performed using the quartile values. The proportional hazard assumptions were checked using the log-log survival plots and by introducing a time-dependent variable into the models.

We also evaluated the impact of major investigational findings on the risk of stroke for patients with and without an ABCD<sup>2</sup> score  $\geq 4$ . Further, in an age-sex- and mRS-adjusted analysis, we identified the predictors of 1-year stroke in the Cox proportional hazard regression models. Variables that were associated with a *P* value of less than .20 with stroke were included in a backward-selection Cox regression analysis using a removal criterium of 0.10. Age, sex, and mRS were forced into the model. Candidate variables were hypertension, diabetes, dyslipidemia, current smokers, former smokers, regular alcohol consumption, regular physical activity, cerebrovascular disease, cardiovascular disease, peripheral artery disease, congestive heart failure (CHF), atrial fibrillation/flutter, socioeconomic factors (living alone, living in rural area, unemployment, educational level), BMI, stroke subtype according to the TOAST classification, ABCD<sup>2</sup> score (0-3, 4-5, 6-7), and major investigative findings. The

assumptions of proportional hazards were checked by introducing time-dependent variables into the model. The C-statistics of the final model were calculated.

Finally, due to the missing ABCD<sup>2</sup> scores, acute infarct lesions, and TOAST classification as described in the main paper, we performed a sensitivity analysis using a multiple imputation to handle missing data (*m* = 5 imputation). Statistical testing was performed at the two-tailed  $\alpha$  level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

The results of comparisons between Japanese and non-Japanese Asian patients are shown can be found in the supplemental materials.

## Results

### Baseline Data

Of the 4789 patients enrolled in the TIAregistry.org, 4583 patients were included in the analysis; 173 did not meet inclusion criteria, while 33 lacked follow-up data. Missing data was due in almost all cases to the emergence of another cause for their TIA-like event. Of the remaining 4583 patients, 345 (7.5%) patients were Japanese (mean age, 66  $\pm$  13 years; 60% men). Ethnically non-Japanese patients identified as European native (*n* = 3317), Eastern Asian (*n* = 725), Middle or Proximal Eastern and Maghreb (*n* = 69), American Hispanic or Latino (*n* = 63), Black or African American (*n* = 38), and other (*n* = 26). Non-Japanese Asian patients were from China (*n* = 518), Korea (*n* = 99), Taiwan (*n* = 66), Thailand (*n* = 37), and Malaysia (*n* = 5).

Table 1 presents the baseline characteristics of the 2 groups of patients. The following characteristics were significantly different between the two groups: the Japanese patient population was older and featured more men, current smokers, and regular drinkers of alcohol; hypertension, dyslipidemia, and coronary artery disease were more common among non-Japanese patients. Comparisons in baseline characteristics between Japanese patients and non-Japanese Asian patients are shown in

**Table 1.** Risk-factor profiles for Japanese and non-Japanese patients

Risk factor	Japanese	Non-Japanese	<i>P</i> value
Age, mean (SD), years	68 (13)	66 (11)	.002
Male	245 (71.0%)	2510 (59.3%)	<.001
Hypertension	224 (64.9%)	2950 (69.9%)	<.001
Diabetes	73 (21.2%)	806 (19.1%)	.94
Dyslipidemia	177 (51.3%)	3017 (71.4%)	<.001
Current smoker	93 (27.0%)	891 (21.4%)	.02
Regular alcohol drinker	133 (38.5%)	780 (18.8%)	<.001
Regular physical activity	88 (25.7%)	891 (22.1%)	.17
Coronary artery disease	30 (8.7%)	535 (12.7%)	.005
Peripheral artery disease	9 (2.6%)	120 (2.9%)	.40
Atrial fibrillation or flutter	99 (11.3%)	349 (8.3%)	.19
Congestive heart failure	8 (2.3%)	116 (2.7%)	.37

Supplemental Table 1. The age was older, male was more common, dyslipidemia was less common, and regular alcohol consumption, history of stroke or TIA, peripheral artery disease, and atrial fibrillation or flutter were more common among Japanese patients as compared to non-Japanese Asian patients.

Regarding baseline brain imaging, computed tomography (CT) was more frequently performed among non-Japanese patients. Diffusion-weighted magnetic resonance imaging (DW-MRI) was performed among the majority of Japanese patients; this was not the case for non-Japanese patients (Table 2). The prevalence of acute infarct was higher among Japanese patients than their non-Japanese counterparts. Intracranial vascular imaging was also more frequently performed among Japanese patients, and intracranial arterial stenosis was more common among Japanese patients. Conversely, Japanese patients featured a lower prevalence of extracranial stenosis  $\geq 50\%$ , despite extracranial arterial imaging having been performed to a similar extent across both patient groups.

In comparison with non-Japanese Asian patients, brain MRI and vascular imaging were more frequently performed among Japanese patients (Supplemental Table 2). The prevalence of acute infarct was higher among Japanese patients than non-Japanese Asian patients. Both intracranial and extracranial arterial stenoses were less common among Japanese patients.

The proportion of mRS 1 was higher among Japanese patients than non-Japanese patients (Table 2). The proportion of mRS 1 was also higher among Japanese patients than non-Japanese Asian patients (Supplemental Table 2). Higher ABCD<sup>2</sup> scores ( $\geq 6$ ) were more common among Japanese patients. They were also more common among

them when compared with non-Japanese Asian patients (28.7% versus 19.8%). As for the type of triage, the proportion of patients examined in a stroke unit or emergency department was higher among Japanese patients, while the proportion of patients examined in a day clinic (TIA clinic) was lower among Japanese patients than among non-Japanese patients. Type of triage could not be compared between Japanese patients and non-Japanese Asian patients because of many missing data among non-Japanese Asian patients.

There were also significant differences between the 2 patient populations in the classification of stroke subtype according to the TOAST assigned at baseline: Japanese patients featured a higher prevalence of small vessel occlusion (SVO) and a lower prevalence of undetermined etiology than did non-Japanese patients (Fig 1). In Japanese patients compared with non-Japanese Asian patients, prevalence of atherothrombotic stroke was lower (24.9% versus 41.6%), cardioembolism was higher (16.2% versus 5.2%), and SVO was comparable (38.3% versus 30.8%) (Supplemental Fig 1).

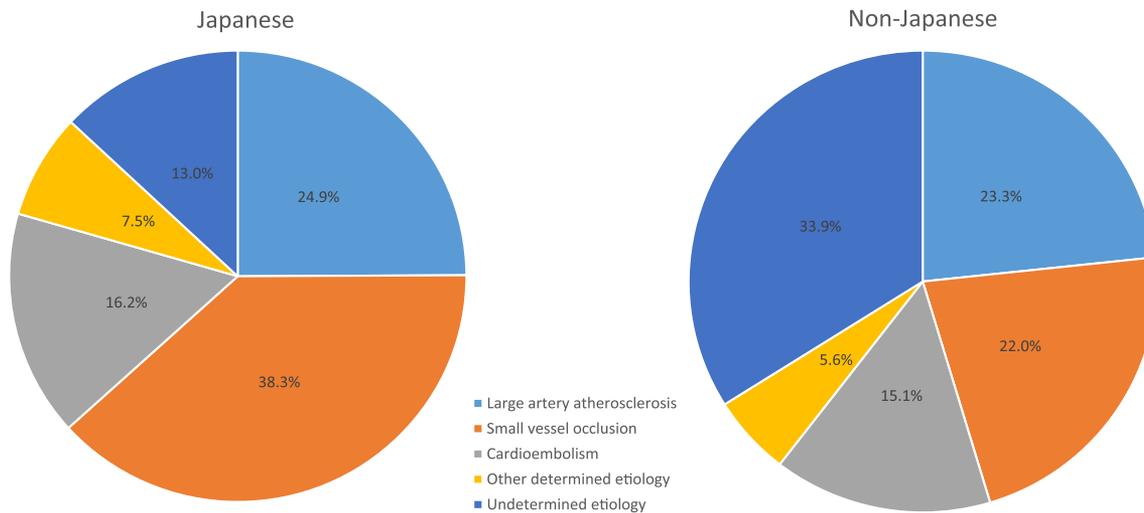
*One-Year Follow-Up Data*

At 1-year follow-up, 274 major cardiovascular events occurred, indicating an event rate of 6.2% (95% CI, 5.5%-7.0%). Kaplan-Meier estimates were 5.9% for non-Japanese patients and 9.0% for Japanese patients (log-rank,  $P = .02$ ). The event rate adjusted for age, sex, and mRS was 7.7% and 6.0% among Japanese and non-Japanese patients, respectively (Table 3); this difference was nonsignificant. However, the rate of nonfatal stroke was higher and the rate of TIA was lower in Japanese patients than in

**Table 2.** Baseline characteristics of Japanese and non-Japanese patients

	Japanese	Non-Japanese	P value
Brain CT	201 (58.3%)	3601 (80.5%)	<.001
Brain MRI (DWI)	343 (99.4%)	2336 (55.1%)	<.001
Acute infarct on CT or MRI	255 (73.9%)	1215 (29.8%)	<.001
Intracranial vascular imaging	342 (99.1%)	3317 (81.7%)	<.001
Intracranial arterial stenosis $\geq 50\%$	67 (19.6%)	424 (12.9%)	.01
Extracranial vascular imaging	318 (92.2%)	3710 (91.1%)	.76
Extracranial arterial stenosis $\geq 50\%$	37 (11.6%)	581 (15.8%)	.003
Modified Rankin scale score			<.001
0	141 (41.5%)	2981 (72.1%)	
1	199 (58.5%)	1154 (27.9%)	
ABCD <sup>2</sup> score			.02
0-3	63 (20.1%)	1231 (34.4%)	
4-5	161 (51.3%)	1690 (47.3%)	
6-7	95 (28.6%)	655 (18.3%)	
Type of triage			<.001
Stroke unit	205 (59.4%)	1758 (41.5%)	
Emergency department	105 (30.4%)	1451 (17.6%)	
Day clinic	3 (0.9%)	744 (17.6%)	
Outpatient clinic	32 (9.3%)	285 (6.7%)	

CT, computerized tomography; DWI, diffusion-weighted image; MRI, magnetic resonance imaging.



**Figure 1.** Trial of Org 10172 in acute stroke treatment (TOAST) classification at baseline of Japanese and non-Japanese patients. Proportions of TOAST subtypes of ischemic stroke were significantly different between Japanese and non-Japanese patients with TIA or minor stroke. Small vessel occlusion was more common among Japanese patients, while undetermined etiology was more common in non-Japanese patients.

non-Japanese patients (Table 3). The rate of nonfatal stroke was also higher in Japanese than in non-Japanese Asian patients (Supplemental Table 2).

As shown in Figure 2, the 2-day risk of stroke was similar between the 2 patient populations. However, the 7-day, 30-day, 90-day, and 12-month risks of stroke were higher among Japanese patients. Data regarding risk of stroke at 7-, 30-, and 90-days were not available among non-Japanese Asian patients.

The age, sex, and mRS adjusted hazard ratio of 1-year stroke among Japanese and non-Japanese patients according to baseline characteristics are presented in Table 4. Significant risk factors for Japanese patients were diabetes

and regular alcohol consumption; those in the non-Japanese population included age, sex (men), history of smoking, and a history of stroke or TIA. There were no significant risk factors at baseline for 1-year stroke among non-Japanese Asian patients (Supplemental Table 3). Risk of 1-year stroke according to the TOAST classification for both Japanese and non-Japanese patients was significantly higher in patients with large artery atherosclerosis (LAA) than patients with other subtypes (Table 5). On the other hand, risk of recurrent stroke was higher in non-Japanese Asian patients with cardioembolism (Supplemental Table 5). The multivariate analysis revealed the independent predictors of stroke in the population of Japanese patients to

**Table 3.** Event rates of primary and secondary outcomes among Japanese and non-Japanese patients

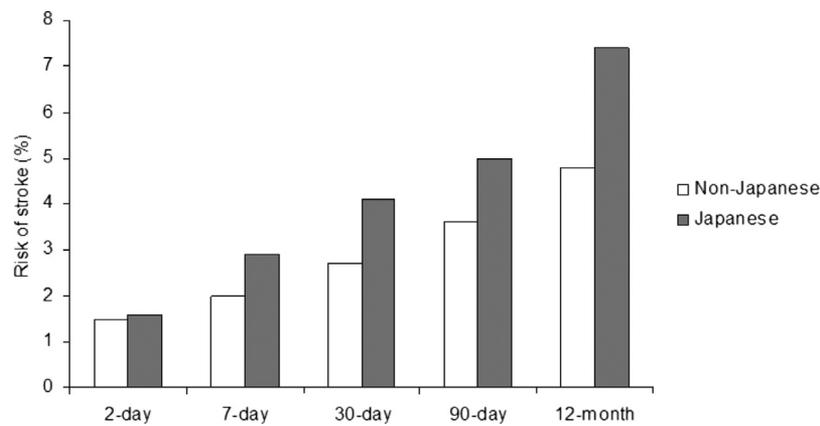
Outcome	Japanese	Non-Japanese	P value*
<b>Primary outcome</b>			
Major cardiovascular events	31 (7.7%)	243 (6.0%)	.18
Cardiovascular death	0 (0.0%)	25 (0.6%)	-
Nonfatal stroke	30 (7.5%)	180 (4.4%)	.008
Nonfatal acute coronary syndrome	1 (0.3%)	38 (1.0%)	-
<b>Secondary outcome</b>			
All-cause mortality	2 (0.5%)	78 (1.9%)	-
Stroke or TIA	39 (11.1%)	494 (12.1%)	.62
Stroke	30 (7.4%)	194 (4.8%)	.03
TIA	10 (3.2%)	316 (7.7%)	.006
Intracerebral hemorrhage	3 (0.8%)	13 (0.3%)	-
Acute coronary syndrome	1 (0.2%)	45 (1.1%)	-
Myocardial infarction	1 (0.2%)	15 (0.4%)	-
Bleeding	9 (2.7%)	78 (2.0%)	.38
Moderately severe bleeding	2 (0.5%)	14 (0.4%)	-
Major bleeding	3 (0.9%)	15 (0.4%)	-

TIA, transient ischemic attack.

Event rate and P value were adjusted for age, sex, and modified Rankin scale score.

Some comparisons were not calculable because of low event rates.

\*Adjusted for age, sex, and modified Rankin Scale score.



**Figure 2.** Short- to long-term stroke rate among Japanese and non-Japanese patients with TIA or minor stroke. The 2-day risk of stroke was similar between Japanese and non-Japanese patients, while the 7-day, 30-day, 90-day, and 12-month risks of stroke were higher among Japanese patients.

**Table 4.** Risk of 1-year stroke by baseline characteristics among Japanese and non-Japanese patients

Baseline characteristic	Japanese		Non-Japanese	
	HR (95% CI)*	P value	HR (95% CI)*	P value
Age, year	10.1 (0.98-1.05)	.44	1.02 (1.01-1.03)	.002
Men	1.44 (0.62-3.38)	.43	1.44 (1.06-1.94)	.018
Hypertension	1.72 (0.79-3.75)	.17	1.05 (0.77-1.43)	.76
Diabetes	2.28 (1.06-4.90)	.03	1.31 (0.93-1.84)	.12
Dyslipidemia	1.23 (0.54-2.80)	.62	1.06 (0.78-1.44)	.72
Former smoker	0.88 (0.38-2.02)	.76	0.68 (0.47-0.98)	.04
Current smoker	1.31 (0.55-3.09)	.54	1.31 (0.91-1.88)	.15
Regular alcohol consumption	2.58 (1.15-5.78)	.02	1.12 (0.79-1.61)	.52
Regular physical activity	0.74 (0.30-1.84)	.54	0.98 (0.69-1.40)	.91
Stroke or TIA	1.47 (0.69-3.16)	.32	1.51 (1.09-2.11)	.014
Coronary artery disease	2.13 (0.79-5.79)	.13	0.90 (0.59-1.38)	.64
Peripheral artery disease	1.39 (0.19-10.27)	.75	0.80 (0.33-1.95)	.62
Atrial fibrillation or flutter	0.82 (0.25-2.74)	.75	1.29 (0.82-2.03)	.26
Congestive heart failure	3.17 (0.75-13.30)	.11	0.86 (0.35-2.09)	.73

CI; confidence interval; HR; hazard ratio; TIA, transient ischemic attack.

\*Adjusted for age, sex, and modified Rankin scale score.

**Table 5.** Risk of 1-year stroke by TOAST classification among Japanese and non-Japanese patients

TOAST classification	Recurrent stroke among Japanese		Recurrent stroke among non-Japanese	
	N (%)	HR (95% CI)*	N (%)	HR (95% CI)*
Large artery disease	12 (48.0%)	8.35 (1.1-63.43)	65 (40.4%)	2.31 (1.56-2.25)
	4 (16.0%)		23 (14.3%)	
Small vessel occlusion	2 (8.0%)	2.89 (0.36-23.33)	28 (17.4%)	1.31 (0.83-2.05)
	4 (24.0%)		12 (3.7%)	
Cardioembolism	2 (8.0%)	1.56 (0.14-17.36)	28 (17.4%)	1.59 (0.99-2.56)
	4 (24.0%)		12 (3.7%)	
Other determined cause	4 (24.0%)	7.66 (0.98-69.13)	12 (3.7%)	1.31 (0.61-2.79)
	1 (4.0%)		12 (3.7%)	
Undetermined etiology	1 (4.0%)	1.00 (reference)	12 (3.7%)	1.00 (reference)
	1 (4.0%)		12 (3.7%)	

CI, confidence interval; HR, hazard ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

\*Adjusted for age, sex, and modified Rankin scale score.

**Table 6.** Predictor of 1-year stroke among Japanese and non-Japanese patients

Predictor	HR (95% CI)*	P value
Japanese		
Prior congestive heart failure	6.08 (1.28-28.81)	.02
Current alcohol consumption	2.28 (1.02-5.17)	.04
Diabetes	2.20 (0.92-4.35)	.08
Non-Japanese		
Previous stroke or TIA	1.65 (1.04-2.60)	.03
ABCD <sup>2</sup> score 6-7	2.09 (1.19-3.69)	.01
Acute infarct	1.65 (1.08-2.52)	.02
Intracranial arterial stenosis $\geq$ 50%	1.68 (1.07-2.64)	.02
Extracranial arterial stenosis $\geq$ 50%	1.69 (1.10-2.61)	.02
Atrial fibrillation	1.68 (0.94-2.99)	.08

CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack.

\*Cox proportional hazard regression model.

be prior CHF and regular alcohol consumption; those for non-Japanese patients included previous stroke or TIA, an ABCD<sup>2</sup> score of 6-7, acute infarct, and intracranial and extracranial arterial stenosis (Table 6). Predictors of stroke in non-Japanese Asian patients were living in a rural area (HR 4.96, 95% CI 1.07-22.94,  $P = .04$ ) and ABCD<sup>2</sup> score 6-7 (HR 4.81, 95% CI 1.00-23.14,  $P = .05$ ).

## Discussion

### Baseline Data

Differences in the risk factor profiles of Japanese and non-Japanese patients in this study were similar to those between Japanese and Western patients reported in the REACH registry,<sup>9</sup> which may affect the risk of stroke or other cardiovascular events as well as the proportion of stroke subtypes. There were also some differences between Japanese and non-Japanese Asian patients. Many of these differences appear to be related to differences in the levels of risk factor management and medical resources.

The present study found that the prevalence of acute infarct was higher among Japanese patients than non-Japanese patients. This finding may have been influenced by brain imaging. DW-MRI, which features a much higher sensitivity to acute ischemic lesions than does CT, was performed in 99.4% of Japanese patients but only in 55.1% of non-Japanese patients; the higher rates of DW-MRI performance for patients with AIS and acute TIA promotes early diagnosis in Japan. The observation of more prevalent AIS and higher ABCD<sup>2</sup> scores, conditions associated with acute infarct, among Japanese TIA patients relative to their non-Japanese counterparts may provide an alternative explanation. It is well recognized that intracranial arterial stenosis is more common and extracranial arterial stenosis is less common in Asian populations than in Western populations. The results of this study were therefore consistent with the previously reported distribution of arterial stenosis.<sup>10,11</sup> In comparison with non-Japanese Asian patients, brain MRI and vascular imaging were also

more frequently performed among Japanese patients. This difference may explain at least in part by the higher prevalence of acute infarct as well as higher ABCD<sup>2</sup> scores among Japanese patients compared to non-Japanese Asian patients. It is interesting that both intracranial and extracranial arterial stenoses were less common among Japanese patients. Whether these differences between Japanese and non-Japanese Asian patients can be explained by the differences in the management of risk factors has yet to be elucidated.

The most remarkable difference between the 2 groups was the higher proportion of Japanese patients with a Rankin score of 1. ABCD<sup>2</sup> scores  $\geq$  6 were more common among Japanese patients as well. A Rankin score of 1 and ABCD<sup>2</sup> scores  $\geq$  6 were more common in Japanese also when compared to non-Japanese Asian patients. These findings suggest that unlike patients with AIS, those with TIA, particularly patients with lower ABCD<sup>2</sup> scores, were overlooked and thus could not access stroke specialists in Japan. The low proportion of TIA clinics that receive patients regardless of the day or time in the triage of Japanese patients may contribute to this trend.<sup>12</sup> Another explanation would be that more patients with TIA mimic were misdiagnosed with true TIA among non-Japanese patients as well as non-Japanese Asian patients as compared to Japanese patients. It has been reported that ABCD<sup>2</sup> score is also useful for the differential diagnosis from TIA mimics, and higher ABCD<sup>2</sup> score is associated with higher probability of true TIA.<sup>13</sup> According to a meta-analysis of 29 studies involving 13,766 TIA patients, the ABCD<sup>2</sup> score does not reliably discriminate those at low and high risk of early recurrent stroke, identify patients in need of urgent intervention, or streamline clinic workload.<sup>14</sup> The study further recommended that stroke prevention services require adequate capacity for the prompt, specialized clinical assessment of all suspected TIA patients for correct patient management.

There were also differences in the classification of stroke subtype according to the TOAST at baseline between

Japanese and non-Japanese patients. The former featured a higher prevalence of SVO and a lower prevalence of undetermined etiology when compared with non-Japanese patients. Previous studies reported that the proportion of lacunar stroke among cases of ischemic stroke is higher among Japanese patients than Western patients.<sup>15,16</sup> The prevalence of atherothrombotic stroke has increased in recent years, although the results of this study suggest that the proportion of lacunar stroke is still high among Japanese patients relative to non-Japanese patients. The lower prevalence of undetermined etiology among Japanese patients may be due to the results of extensive investigations into the causes of stroke; Japanese stroke centers employ sensitive brain and vascular imaging as well as transesophageal echocardiography as routine clinical practice. In Japanese patients compared to non-Japanese Asian patients, prevalence of atherothrombotic stroke was lower, cardioembolism was higher, and SVO was comparable. Lower prevalence of atherothrombotic stroke can be explained by lower prevalence of not only extracranial but also intracranial arterial stenosis in Japanese compared to non-Japanese Asian patients. Higher prevalence of cardioembolism can be explained by higher prevalence of atrial fibrillation probably due to more extensive investigation of covert atrial fibrillation in Japanese patients compared with non-Japanese Asian patients.

#### *One-Year Follow-Up Data*

There were no significant differences in primary outcomes after adjustments for age, sex, and mRS. The adjusted event rate was 7.7% in Japanese patients and 6.0% in non-Japanese patients; the difference was not statistically significant. However, the rates of nonfatal-stroke were higher and the rate of TIA was lower among Japanese patients. This finding may be accounted for by the high prevalence of acute infarct and elevated ABCD<sup>2</sup> scores among Japanese patients relative to non-Japanese patients. Prevalence of acute infarct was higher in Japanese patients than in non-Japanese and non-Japanese Asian patients. It is generally accepted that risk of recurrent stroke is higher in patients with ischemic stroke than in TIA patients.<sup>17</sup> It is well known that TIA is a prodromal syndrome most common among patients with LAA than those with other subtypes of ischemic stroke.<sup>18</sup> We also reported that a history of TIA is more common among patients with LAA than those with SVO or cardioembolism.<sup>19</sup> A higher proportion of patients with SVO was observed in the Japanese-patient population than in the population of non-Japanese patients at baseline. This finding may partially account for the lower incidence of TIA among Japanese patients and may also account for the similar incidence of TIA among non-Japanese Asian patients.

The 2-day risk of stroke was similar between Japanese and non-Japanese patients, while the 7-day, 30-day,

90-day, and 12-month risks of stroke were significantly higher among the former than the latter. In the Asian sub-analysis of TIAregistry.org, rate of recurrent stroke was lower at 2 days and 6 days, but higher at 90 days and 12 months among Asian patients relative to non-Asian patients. The reason why Japanese and other Asian patients featured a lower risk of stroke immediately following TIA or minor stroke and a higher risk at later periods than did non-Asian patients remains to be elucidated. The higher proportion of SVO and a lower proportion of extracranial arterial stenosis among Japanese patients may account for this trend; ACVS with severe carotid stenosis may elevate the risk of stroke during the very early period following TIA or minor stroke than those without carotid stenosis.<sup>20</sup> Another possibility may involve the significantly lower rate of statin prescription at discharge to Japanese patients than to non-Japanese patients (46.5% versus 67.5%,  $P < .001$ ). The rate of antiplatelet-drug prescription to Japanese patients at discharge was also slightly lower (82.5% versus 90.2%,  $P < .001$ ). However, the prescription rate of antihypertensive drugs was similar in both populations (63.5% versus 67.7%,  $P = .08$ ). The differences in prescription rates between Japanese and non-Japanese patients continued at 12 months (statin, 49.0% versus 64.0%,  $P < .001$ ; antiplatelet drugs, 74.1% versus 77.0%,  $P = .027$ ; and antihypertensive drugs, 71.7% versus 68.6%,  $P = .90$ ). Treatment with statin may contribute to reducing the later risk of stroke after TIA or minor stroke.<sup>21</sup>

Significant baseline risk factors of recurrent stroke among Japanese patients included diabetes and regular alcohol consumption; these two risk factors were more common in Japanese patients. On the other hand, hypertension and dyslipidemia are less common among Japanese patients. The differences in the prevalence of baseline risk factors may be associated with the differences in their impact on the risk of subsequent stroke. The aforementioned results suggest that stricter control of diabetes and regular alcohol consumption is required for secondary prevention of stroke among Japanese ACVS patients. Recent evidence of the J-DOIT 3 showed that multiple aggressive interventions dramatically reduced the risk of stroke in comparison with conventional treatments administered to Japanese diabetes patients.<sup>22</sup> In Western populations, moderate alcohol drinking may reduce the risk of ischemic stroke.<sup>23</sup> However, this J-shaped association is not obvious in Japanese populations.<sup>24,25</sup> One possible explanation is that alcohol is more toxic to Japanese patients. It is known that 41%-52% of the Japanese population possesses the ALDH2\*2 allele, including the 1%-8% who are homozygous for ALDH2\*2: a gene that diminishes the metabolism of acetaldehyde into acetate, leading to an excessive build-up of acetaldehyde and an increase in the response to alcohol.<sup>26,27</sup> The reduced ability to metabolize acetaldehyde is common not only in the Japanese population but also in other East Asian

populations<sup>27</sup>; hence, current; alcohol consumption was an independent predictor for stroke in the Asian subanalysis of TIAregistry.org as well.<sup>6</sup> Japanese and other East Asian genetic characteristics may therefore increase the effect of alcohol on stroke. Unfortunately, the amount of alcohol intake could not be analyzed because of the dearth of this information in the data. Regular alcohol drinking was not a risk factor for recurrent stroke, although regular alcohol drinkers were less common in non-Japanese Asian patients, which may account for this result.

Risk of 1-year stroke according to the TOAST classification among Japanese patients was significantly higher in patients with LAA than those with other subtypes. The complete analysis of TIAregistry.org has already been demonstrated that the risk of stroke and other vascular events was higher in patients with LAA than those with other subtypes.<sup>5</sup> Therefore, strategies to reduce the residual risk of atherothrombotic stroke are warranted not only in Western populations but also in Japanese populations. We have demonstrated that the risk of vascular events remains elevated even after the completion of a revascularization procedure with carotid endarterectomy or stenting in patients registered in TIAregistry.org.<sup>28</sup> Atherothrombosis is a polyvascular disease, and local endovascular intervention does not reduce the risk of systemic vascular events. Therefore, total management in tandem with multiple interventions is required for the prevention of stroke and other vascular events in patients with LAA. Risk of recurrent stroke was higher in non-Japanese Asian patients with cardioembolism, which suggests inadequate use and control of anticoagulants in this population.

The multivariate analysis revealed that independent predictors of stroke among Japanese patients included prior CHF and current alcohol consumption. CHF is a common disease and major risk factor for ischemic stroke.<sup>29,30</sup> Data from previous cohort studies indicated that the risk of ischemic stroke is 2-3 times higher among patients with CHF than those without CHF.<sup>31,32</sup> It is likely that CHF-related strokes are primarily embolic, but concurrent subtypes of stroke must be taken into account. The number of CHF patients is rising with the increase in the elderly population. Higher mean age in Japanese patients compared with non-Japanese patients and non-Japanese Asian patients may contribute to the increased risk of CHF-induced recurrent stroke.<sup>33</sup> Stroke prevention in patients with CHF will become a more urgent, global issue worldwide along with increasing of elderly population. Previous stroke or TIA, an ABCD<sup>2</sup> score of 6-7, acute infarct, and intracranial and extracranial arterial stenosis were independent predictors for subsequent stroke in the analysis of all the patients registered in the TIAregistry.org. Our subanalysis revealed that these factors were positive predictors for non-Japanese patients but not Japanese patients. The small sample of Japanese patients relative to that of non-Japanese patients and the consequent

diminished power of the present study may account for the irrelevance of these predictors to Japanese patients; the predictors are well-known risk factors for recurrent stroke in TIA patients, regardless of ethnicity or region.<sup>1,5,6</sup> We need to collect data on a larger number of Japanese patients with ACVS to identify these risk factors in future studies.

### Study Limitations

The present study is subject to limitations inherent to an observational study. Even after extensive adjustment, residual confounding cannot be ruled out. In addition, because participating sites were not selected at random, the cohort analyzed in this study could differ from those of the general TIA/stroke population. This study was further constrained by missing data; of the 4583 initially included patients, 383 (8.4%) were lost to follow-up. The relatively small sample of Japanese patients may have caused type II errors in our statistical analysis, accounting for our findings of the negative risk factors and predictors. Additionally, considerable numbers of missing data made it impossible to statistically compare certain factors between Japanese and non-Japanese Asian patients.

### Conclusions

The present investigation identified considerable differences in risk factors, stroke subtypes, and outcome events between Japanese and non-Japanese patients. Significant baseline risk factors of recurrent stroke were diabetes and regular alcohol consumption in Japanese patients. Risk of 1-year stroke according to the TOAST classification among Japanese patients was significantly higher in patients with LAA than those with other subtypes. Predictors of recurrent stroke among Japanese patients included prior CHF and alcohol consumption. Strategies to attenuate the residual risk of stroke independent of current optimal treatment guidelines should take these Japanese-patient specific findings into account.

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### Supplementary materials

Supplementary data to this article can be found online at doi:[10.1016/j.jstrokecerebrovasdis.2019.05.005](https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.005).

### References

1. Uchiyama S. The concept of acute cerebrovascular syndrome. In: Uchiyama S, Amarenco P, Minematsu K, Wong KSL, eds. *TIA as acute cerebrovascular syndrome*, Basel: Karger Publishers; 2014:11-18.
2. Uchiyama S. TIA as acute cerebrovascular syndrome. *J Neurol Disord Stroke* 2017;5:1121-1126.

3. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. *Neurology* 2005;64:817-820.
4. Johnston SC, Nguyen-Huynh MN, Schwarz ME, et al. National Stroke Association guidelines for the management of transient ischemic attacks. *Ann Neurol* 2006;60:301-313.
5. Amarenco P, Lavallee PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med* 2016;374:1533-1542.
6. Hoshino T, Uchiyama S, Wong LKS, et al. Differences in characteristics and outcomes between Asian and non-Asian patients in the TIAregistry.org. *Stroke* 2017;48:1779-1787.
7. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. *Stroke* 1993;24:35-41.
8. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-682.
9. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-189.
10. Sacco RL, Kargman DE, Gu Q, et al. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. *Stroke* 1995;26:14-20.
11. Rockman CB, Hoang H, Guo Y, et al. The prevalence of carotid artery stenosis varies significantly by race. *J Vasc Surg* 2013;57:327-337.
12. Lavallée PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet Neurol* 2007;6:953-960.
13. Sheehan OC, Merwick A, Kelly LA, et al. Diagnostic usefulness of the ABCD<sup>2</sup> score to distinguish transient ischemic attack and minor ischemic stroke from noncerebrovascular events: the North Dublin TIA study. *Stroke* 2009;40:3449-3454.
14. Wardlaw JM, Brazzelli M, Chappell FM, et al. ABCD2 score and secondary stroke prevention. Meta-analysis and effect per 1,000 patients triaged. *Neurology* 2015;85:373-380.
15. Kubo M, Hata J, Doi Y, et al. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. *Circulation* 2008;118:2672-2678.
16. Turin TC, Kita Y, Rumana N, et al. Ischemic stroke subtypes in a Japanese population: Takashima Stroke Registry, 1988-2004. *Stroke* 2010;41:1871-1876.
17. Coull AJ, Lovett JK, Rothwell PM. Oxford Vascular Study: Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organization of services. *BMJ* 2004;328:326.
18. Sacco RL. Risk factors for TIA and TIA as a risk factor for stroke. *Neurology* 2004;6:S7-S11.
19. Hoshino T, Mizuno S, Shimizu S, et al. Clinical features and functional outcome of stroke after transient ischemic attack. *J Stroke Cerebrovasc Dis* 2013;22:260-266.
20. Purroy F, Montaner J, Molina CA, et al. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. *Stroke* 2007;38:3225-3229.
21. Merwick A, Albers GW, Arsava EM, et al. Reduction in early stroke risk in carotid stenosis with transient ischemic attack associated with statin treatment. *Stroke* 2013;44:2814-2820.
22. Ueki K, Sasako T, Okazaki Y, et al. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT 3): an open-label, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:951-964.
23. Sacco RL, Elkind M, Borden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA* 1999;281:53-60.
24. Camargo Jr CA. Moderate alcohol consumption and stroke. The epidemiologic evidence. *Stroke* 1989;20:1611-1626.
25. Iso H, Baba S, Mannami T, et al. Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. *Stroke* 2004;35:1124-1129.
26. Amamoto K, Okumura T, Tamaki S, et al. Epidemiologic study of the association of low-Km mitochondrial acetaldehyde dehydrogenase genotypes with blood pressure level and the prevalence of hypertension in a general population. *Hypertens Res* 2002;25:857-864.
27. Eng MY, Luczak SE, Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. *Alcohol Res Health* 2007;30:22-27.
28. Hobeau C, Lavallee PC, Rothwell PM, et al. Symptomatic patients remain at substantial risk of arterial disease complications before and after endarterectomy or stenting. *Stroke* 2017;48:1005-1010.
29. Lloyd-Jones D. Heart disease and stroke statistics-2010 update. *Circulation* 2010;12:e46-e215.
30. Haeusler K, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke* 2011;42:2977-2982.
31. Kannel WB, Wolf PA, Verter L. Manifestation of coronary disease predisposing stroke: the Framingham Study. *J Am Med Assoc* 1983;250:2942-2946.
32. Witt BJ, Brown RD, Jacobssen SJ, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J* 2006;152:102-109.
33. Iguchi M, Tezuka Y, Ogawa H, et al. Incidence and risk factors of stroke or systemic embolism in patients with atrial fibrillation and heart failure. The Fushimi AF Registry. *Circ J* 2018;82:1327-1335.