Differences in Characteristics and Outcomes Between Asian and Non-Asian Patients in the TIAregistry.org

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Background and Purpose—This study provides the contemporary causes and prognosis of transient ischemic attack (TIA) and minor stroke in Asians and the direct comparisons with non-Asians.

Methods—The TIAregistry.org enrolled 4789 patients (1149 Asians and 3640 non-Asians) with a TIA or minor ischemic stroke within 7 days of onset. Every participating facility had systems dedicated to urgent intervention of TIA/stroke patients by specialists. The primary outcome was a composite of cardiovascular death, nonfatal stroke, and nonfatal acute coronary syndrome.

Results—Approximately 80% of patients were evaluated within 24 hours of symptom onset. At 1 year, there were no differences in the rates of composite cardiovascular events (6.8% versus 6.0%; P=0.38) and stroke (6.0% versus 4.8%; P=0.11) between Asians and non-Asians. Asians had a lower risk of cerebrovascular disease (stroke or TIA) than non-Asians (adjusted hazard ratio, 0.79; 95% confidence interval, 0.63–0.98; P=0.03); the difference was primarily driven by a lower rate of TIA in Asians (4.2% versus 8.3%; P<0.001). Moderately severe bleeding was more frequent in Asians (0.8% versus 0.3%; P=0.02). In multivariable analysis, multiple acute infarcts (P=0.005) and alcohol consumption (P=0.02) were independent predictors of stroke recurrence in Asians, whereas intracranial stenosis (P<0.001), ABCD^2 score (P<0.001), atrial fibrillation (P=0.008), extracranial stenosis (P=0.03), and previous stroke or TIA (P=0.03) were independent predictors in non-Asians.

Conclusions—The short-term stroke risk after a TIA or minor stroke was lower than expected when urgent evidence-based care was delivered, irrespective of race/ethnicity or region. However, the predictors of stroke were different for Asians and non-Asians. **(*Stroke*. 2017;48:1779-1787. DOI: 10.1161/STROKEAHA.117.016874.)**

Key Words: ischemic stroke ■ population ■ prognosis ■ race and ethnicity ■ transient ischemic attack

Approximately 15 million people have strokes worldwide each year. Up to 9 million are Asians,[1] with the number continuing to increase, especially in low- to middle-income countries.[2] Therefore, any improvement in prevention and management of stroke in Asia is crucial for global health.

Recently, there have been major changes in the management strategy of transient ischemic attack (TIA). The importance of urgent evidence-based intervention for TIA patients in specialized units has been emphasized because this can markedly reduce the risk of subsequent stroke by 80%,[3,4] leading to a

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substantial reduction in stroke-related disability and mortality and consequent reduction in healthcare costs.[5] Based on these advances in care, the TIAregistry.org was designed to reassess the contemporary profile, risk stratification, and prognosis of patients with TIA and minor stroke.[6] A strength of this study was that a large number of patients across the world were accrued with detailed clinical information and assessed using standardized methodology. Given the considerable racial–ethnic differences in stroke (eg, risk factors, stroke subtypes, genetic background, diet, lifestyle, socioeconomic status, stroke care system, and prognosis),[7] investigations of stroke by race/ethnicity are important for developing targeted population-specific management strategies, as well as projecting resource requirements for stroke care. However, few such data have been available from Asia and non-Asia together in a same study, and the racial–ethnic differences in the nature and impact of TIA remain to be elucidated. The aim of this study was to describe and compare the prognosis of TIA in Asians and non-Asians in the context of the modern development of care system.

Methods

The detailed design and primary results of the TIAregistry.org have been reported elsewhere.[6] Briefly, the TIAregistry.org was an international, prospective, observational registry that enrolled 4789 patients with TIA or minor stroke within 7 days of onset, between June 2009 and December 2011. The protocol was approved by local institutional review boards. Eligible patients had focal brain ischemia with resolution of symptoms or a minor ischemic stroke with a modified Rankin Scale of 0 or 1 when first evaluated by a stroke specialist. The selected facilities were based in 21 countries and had a dedicated TIA/stroke patient care system staffed by stroke specialists, with a volume of at least 100 patients annually during the previous 3 years. The acute care settings included emergency departments, stroke units, day clinics, and outpatient clinics. Patients were classified as Asian origin (n=1149) if they were recruited from China (n=448), Hong Kong (n=139), India (n=5), Japan (n=345), Korea (n=101), Malaysia (n=6), or Taiwan (n=105) and as non-Asian origin (n=3640) from other countries (Appendix in the online-only Data Supplement).

Stroke specialists prospectively collected patient data, using a standardized web-based case report form, at the time of evaluation of the qualifying event (baseline), at 1, 3, and 12 months after baseline (the period of analysis for the current study), and every 12 months thereafter for 5 years. The baseline data included clinical symptoms, medical history, living and socioeconomic indicators, physical examinations, investigations (including standard blood chemistry, brain and cerebral artery imagings, and cardiac work-up), and management (medical treatment and revascularization procedure). An etiologic subtype was assigned to each patient according to the TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment).[8] In cases with no infarct on brain imaging, small-vessel disease was diagnosed when the patient had clinical symptoms, suggesting lacunar syndrome (eg, pure hemiparesis, pure hemisensory loss, ataxic hemiparesis, dysarthria-clumsy hand syndrome) without proximal arterial stenosis, cardioembolic sources, and other definitive causes for the event.

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 recurrence, all-cause mortality, and bleeding. Bleeding was categorized according to the GUSTO definition (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries).[9] Two of the authors (P.C. Lavallée and P. Amarenco) adjudicated clinical events independently by reviewing the patient's information provided from the site investigators. In cases of discrepancy, the final decision was validated by their consensus.

Statistical Analysis

Quantitative variables were expressed as mean (standard deviation) for normally distributed data or median (interquartile range) otherwise. Qualitative variables were expressed as number (percentage). The normality of distribution was assessed graphically and using the Shapiro–Wilk test. Baseline characteristics, clinical presentation of qualifying event, and investigation findings were compared between Asian and non-Asian patients. All comparisons were adjusted by age and sex using linear regression models for quantitative variables and logistic regression models for qualitative (all binary) variables. For variables with skewed distributions, linear regression analysis was performed using log-transformed values.

The 1-year event rates (primary and secondary end points) were compared between the groups using the Cox proportional hazard model adjusted for age and sex. For a given end point, deaths that were not included in the end point were treated as censored events. Events that occurred after the 1-year follow-up period were not included in the current analysis. Patients from non-Asian countries were used as a reference group in the Cox proportional hazard model to determine hazard ratios (HRs) as effect size measures, with their 95% confidence intervals (CIs). To avoid the bias related to overfitting, only 2 confounding factors (ie, body mass index and modified Rankin Scale) were selected for further adjustments, given their marked disproportions between Asians and non-Asians, as well as their relative impacts on vascular outcomes. The proportional hazard assumptions were checked by examining the Schoenfeld residuals. Cumulative event curves were constructed using the Kaplan–Meier method. Adjusted event rates were calculated using the corrected group prognosis method[10]; adjustment for age was made using quartile values. We calculated the predictive ability of $ABCD^2$ score for 1-year stroke recurrence in Asians and non-Asians by calculating Harrell C statistic.

Cox proportional hazard regression models were used to identify predictors of 1-year stroke in Asian and non-Asian patients separately. Candidate variables were hypertension, diabetes mellitus, dyslipidemia, current smoking, former smoking, regular alcohol consumption, regular physical activity, coronary artery disease, peripheral artery disease, chronic heart failure, atrial fibrillation/flutter, socioeconomic factors, body mass index, atherogenic dyslipidemia (high-density lipoprotein cholesterol ≤40 mg/dL and triglycerides ≥150 mg/dL), TOAST classification, $ABCD^2$ score, and major investigational findings. Heterogeneities in the association of risk factors with stroke risk between Asian and non-Asian patients were tested by formal interaction tests. Because some significant heterogeneity was found, further multivariable analyses were performed in Asians and Non-Asians, separately. Variables associated with stroke with a P value <0.10 in age-adjusted analyses were included in a backward-selection Cox regression analysis using removal criteria of 0.10. Age and sex were forced into the model.

Finally, because there were some missing data, a sensitivity analysis was performed using multiple imputations by chained equations method (n=5; imputed data sets were generated using the above-mentioned candidate variables). In each imputed data, the complete model (ie, containing all significant factors with a P value <0.10) was implemented. Then the 10 estimates coefficients of each variable were combined, and the least significant factor was removed from the model. The process was continued until the final model was obtained.

Statistical testing was performed at the 2-tailed α level of 0.05. Data were analyzed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

A total of 4789 patients from 61 sites in 21 countries were enrolled in the TIAregistry.org; 173 did not meet inclusion criteria and 33 had no follow-up data, leaving 4583 (1070 Asians and 3513 non-Asians) for inclusion in the current analysis (Figure I in the online-only Data Supplement). Table 1 shows baseline characteristics of Asian and non-Asian patients. Nearly 80% of patients in each group were evaluated by a stroke specialist within 24 hours of symptom onset. Asians were younger

Table 1. Baseline Characteristics of Asian and Non-Asian Patients

	Non-Asian (n=3513)	Asian (n=1070)	*P* Value*
Evaluated within 24 h of onset	2766 (78.7)	827 (77.3)	0.26
Demographics			
Age, mean (SD), y	67 (13)	64 (12)	<0.001
Men	2030 (57.8)	725 (68.1)	<0.001
Medical history			
Hypertension	2535 (72.2)	639 (59.7)	<0.001
Diabetes mellitus	651 (18.5)	228 (21.3)	0.52
Dyslipidemia	2503 (71.3)	691 (64.6)	<0.001
Former smokers	905 (26.4)	200 (18.8)	<0.001
Current smokers	670 (19.5)	314 (29.5)	<0.001
Regular alcohol consumption	649 (18.9)	264 (24.9)	0.003
Regular physical activity	731 (21.7)	248 (24.3)	0.68
Stroke, transient ischemic attack	570 (16.3)	233 (21.9)	<0.001
Coronary artery disease	474 (13.5)	91 (8.5)	0.001
Peripheral artery disease	116 (3.3)	13 (1.2)	0.002
Atrial fibrillation/flutter	325 (9.3)	63 (5.9)	0.03
Congestive heart failure	107 (3.1)	17 (1.6)	0.10
Living and socioeconomics indicators			
Living alone	1276 (37.3)	240 (22.9)	<0.001
Living in rural area	571 (16.5)	63 (6.2)	<0.001
Unemployment†	168 (5.0)	66 (6.6)	0.01
Educational level			<0.001
None	161 (5.0)	79 (8.0)	
Primary	1156 (36.1)	233 (23.5)	
Secondary	1384 (43.2)	506 (51.1)	
Examinations			
Body mass index, mean (SD), kg/m^2	27.1 (4.6)	24.7 (4.2)	<0.001
Systolic BP, mean (SD), mm Hg	146 (24)	143 (23)	0.03
Diastolic BP, mean (SD), mm Hg	81 (13)	82 (13)	0.02
Glucose,‡ median (IQR), mg/dL	105 (92–130)	103 (90–125)	0.39
HbA1c,‡ %	5.7 (5.3–6.2)	5.8 (5.4–6.4)	<0.001
LDL cholesterol, mean (SD), mg/dL	120 (40)	116 (35)	0.04
HDL cholesterol, mean (SD), mg/dL	51 (16)	47 (14)	<0.001
Triglycerides,‡ median (IQR), mg/dL	118 (88–165)	119 (88–172)	0.20
Atherogenic dyslipidemia	378 (10.8)	158 (14.8)	0.007
Modified Rankin Scale			<0.001
0 (no symptom)	2552 (73.8)	570 (56.2)	
1 (no significant disability)	908 (26.2)	445 (43.8)	

Data are number (%) unless otherwise indicated. BP indicates blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; and SD, standard deviation.

*Adjusted by age and sex.

†Excluding student, social pensioner on disability grant, and old age pensioner.

‡Analyzed using the logarithmic values.

and more likely to be male, to consume cigarettes and alcohol, and to have previous stroke or TIA and a higher modified Rankin Scale than non-Asians, while non-Asians were more likely to have hypertension, dyslipidemia, previous coronary and peripheral arterial diseases, and atrial fibrillation.

Characteristics of first contact are presented in Table I in the online-only Data Supplement. Although the data were available for only 3109 patients, we found that the time to first contact (to any type of medical attention, including both stroke specialists and nonspecialists) was longer in Asian patients. Approximately 60% of Asians contacted an emergency department in the first instance. Table 2 shows clinical features of the qualifying event and major investigational findings. Motor weakness was the most frequent symptoms in both populations. Aphasia was more frequent in non-Asians. Asians showed a higher ABCD^2 score and higher proportions of large-artery atherosclerosis and small-vessel disease than non-Asians. More than 96% of patients underwent brain imaging; Asians were more likely to have ≥1 acute infarcts (ie, minor stroke by tissue-based definition; 53.1% versus 27.4%; *P*<0.001) and intracranial stenosis (23.9% versus 10.3%; *P*<0.001) than non-Asians.

Table II in the online-only Data Supplement shows preadmission medications and treatments at discharge. At discharge, 90.8% and 17.4% of Asian patients received any antiplatelet and anticoagulant therapy, respectively. Table III in the online-only Data Supplement shows 3-month and 12-month self-reported medications and examination findings. The mean blood pressure and low-density lipoprotein cholesterol levels were similar in both groups.

During a 1-year follow-up period, 274 major vascular events occurred given an event rate of 6.2% (95% confidence interval [CI], 5.5%–7.0%; Table 3), with no statistical difference between Asians and non-Asians (6.8% versus 6.0%; *P*=0.38). As shown in Figure 1, Asians had a lower risk of cerebrovascular disease (stroke or TIA) compared with non-Asians (age- and sex-adjusted HR, 0.79; 95% CI, 0.63–0.98; *P*=0.03); although the stroke rate was similar (6.0% versus 4.8%; *P*=0.11), the TIA rate was significantly lower in Asians (4.2% versus 8.3%; *P*<0.001). The risk of moderately severe bleeding was higher in Asians (age- and sex-adjusted HR, 3.19; 95% CI, 1.18–8.67; *P*=0.02) but was of borderline significance after an additional adjustment for body mass index and modified Rankin Scale (fully adjusted HR, 3.04; 95% CI, 0.93–9.97; *P*=0.07).

Table 2. Clinical Presentation of Qualifying Event and Investigation Findings in Asian and Non-Asian Patients

	Non-Asian (n=3513)	Asian (n=1070)	*P* Value*
Clinical symptoms			
Weakness	1760 (50.6)	707 (69.9)	<0.001
Numbness	564 (16.2)	248 (24.6)	<0.001
Sensory symptoms	1033 (29.8)	196 (19.4)	<0.001
Speech disturbances	1713 (49.4)	448 (44.4)	0.05
Aphasia	740 (21.3)	42 (4.2)	<0.001
Dysarthria	992 (28.6)	400 (39.9)	<0.001
Transient monocular blindness	159 (4.6)	13 (1.3)	<0.001
Vertigo, unsteadiness, gait ataxia	618 (17.6)	155 (14.5)	0.02
Headache	281 (8.1)	46 (4.6)	<0.001
Duration of symptoms			0.21
≤10 min	717 (20.7)	186 (18.1)	
11–60 min	1048 (30.2)	235 (22.8)	
1–24 h	694 (20.0)	178 (17.3)	
>24 h	1011 (29.1)	430 (41.8)	
Prior TIA within 3 mo			
Any prior TIA	449 (12.9)	174 (17.2)	0.02
≥1 prior TIA with similar symptoms	243 (6.9)	97 (9.1)	0.12
$ABCD^2$ score			<0.001
0–3	1075 (35.3)	219 (26.0)	
4–5	1418 (46.5)	433 (51.4)	
6–7	554 (18.2)	191 (22.7)	
TOAST classification			<0.001
Large artery atherosclerosis	670 (20.2)	317 (35.2)	
Small vessel disease	680 (20.5)	303 (33.7)	
Cardioembolism	556 (16.8)	85 (9.4)	
Other determined cause	209 (6.3)	35 (3.9)	
Undetermined	1194 (36.1)	160 (17.8)	
Investigations			
Brain imaging (CT or DWI)	3392 (96.6)	1032 (96.4)	0.99
Acute infarct (single or multiple)	930 (27.4)	548 (53.1)	<0.001
Single acute infarct	621 (18.4)	370 (36.0)	<0.001
Multiple acute infarcts	302 (8.9)	176 (17.1)	<0.001
Extracranial imaging (CT, MRA, or Doppler)	3244 (95.2)	784 (77.5)	<0.001
≥1 stenosis ≥50% or occlusion	480 (14.9)	138 (17.9)	0.03
Intracranial imaging (CT, MRA, or Doppler)	2801 (82.5)	858 (85.0)	0.12
≥1 stenosis ≥50% or occlusion	287 (10.3)	204 (23.9)	<0.001
ECG or 24-h Holter ECG	3120 (92.4)	893 (84.9)	<0.001
Atrial fibrillation/flutter	326 (10.6)	84 (9.5)	0.82
Newly diagnosed atrial fibrillation/flutter	158 (5.1)	41 (4.6)	0.65

Data are number (%). CT indicates computed tomography; DWI, diffusion-weighted imaging; ECG, electrocardiogram; MRA, magnetic resonance angiography; TIA, transient ischemic attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Adjusted by age and sex.

Table 3. One-Year Primary and Secondary Outcomes in Asian and Non-Asian Patients

	Events, n (%)*					
	Non-Asian (n=3513)	Asian (n=1070)	HR (95% CI)*	*P* Value*	HR (95% CI)†	*P* Value†
Primary outcome						
Major cardiovascular events	207 (6.0)	67 (6.8)	1.13 (0.86–1.50)	0.38	1.16 (0.86–1.58)	0.33
Secondary outcomes						
All-cause mortality	70 (2.0)	10 (1.1)	0.53 (0.26–1.07)	0.08	0.49 (0.24–1.03)	0.06
Stroke or transient ischemic attack	432 (12.6)	101 (10.0)	0.79 (0.63–0.98)	0.03	0.85 (0.67–1.08)	0.19
Stroke	164 (4.8)	60 (6.0)	1.28 (0.95–1.72)	0.11	1.25 (0.90–1.74)	0.18
Transient ischemic attack	283 (8.3)	43 (4.2)	0.50 (0.36–0.69)	<0.001	0.57 (0.41–0.80)	0.001
Intracerebral hemorrhage	11 (0.3)	5 (0.5)	1.65 (0.57–4.82)	0.36	NC	NC
Acute coronary syndrome	39 (1.1)	7 (0.7)	0.64 (0.28–1.43)	0.28	0.81 (0.33–1.95)	0.63
Myocardial infarction	11 (0.3)	5 (0.5)	1.62 (0.55–4.71)	0.38	NC	NC
Bleeding	67 (2.0)	20 (2.1)	1.03 (0.62–1.70)	0.91	0.88 (0.50–1.54)	0.66
Moderately severe bleeding	9 (0.3)	7 (0.8)	3.19 (1.18–8.67)	0.02	3.04 (0.93–9.97)	0.07
Major bleeding	12 (0.4)	6 (0.6)	1.76 (0.65–4.74)	0.26	NC	NC

CI indicates confidence interval; HR, hazard ratio; and NC, not calculable.
*Adjusted by age and sex.
†Adjusted by age, sex, body mass index, and modified Rankin Scale.

In Asian patients, the 2-day, 7-day, 30-day, 90-day, and 365-day rates of stroke were 1.0%, 1.7%, 2.9%, 4.1%, and 6.0%, respectively (Figure 2A). Figure 2B and 2C shows the stroke rates according to ABCD^2 score. In Asians, the stroke risk increased gradually with ABCD^2 score, ranging from 0% to 15.1% for 1 year. The predictive ability of the ABCD^2 score was similar between Asians (C statistic, 0.595; 95% CI, 0.513–0.676) and non-Asians (C statistic, 0.596; 95% CI, 0.552–0.640). Table IV in the online-only Data Supplement shows the rate of stroke at 3 and 12 months categorized by ABCD^2 score in Asian patients with and without acute infarction (ie, tissue-based definition of TIA and stroke). Stroke rates at 3 months were similar between tissue-positive events with the lowest ABCD^2 score (0–2; 4.5%; 95% CI, 1.9–10.5) and tissue-negative events with the highest ABCD^2 score (7; 4.2%; 95% CI, 1.4–12.5). Patients with acute infarct had higher ABCD^2 scores than those without (P_{trend}<0.001) (Figure II in the online-only Data Supplement).

Table V in the online-only Data Supplement shows age- and sex-adjusted HRs for stroke recurrence according to

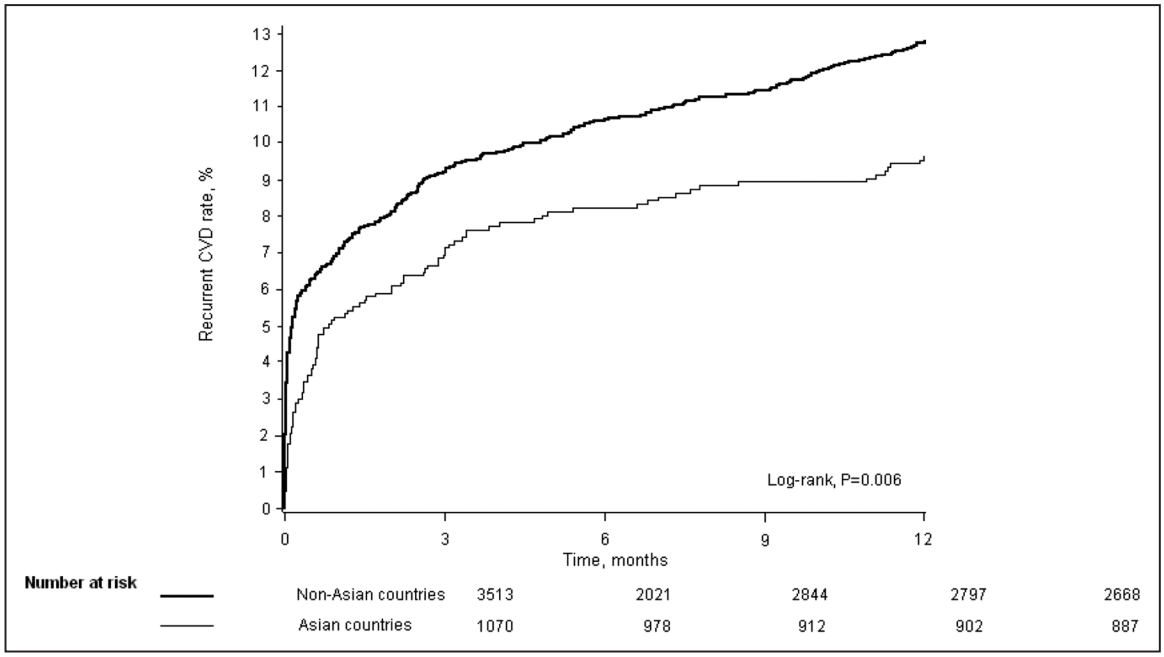

Figure 1. Unadjusted Kaplan–Meier curves for cerebrovascular events in Asian and non-Asian patients. CVD indicates cerebrovascular disease.

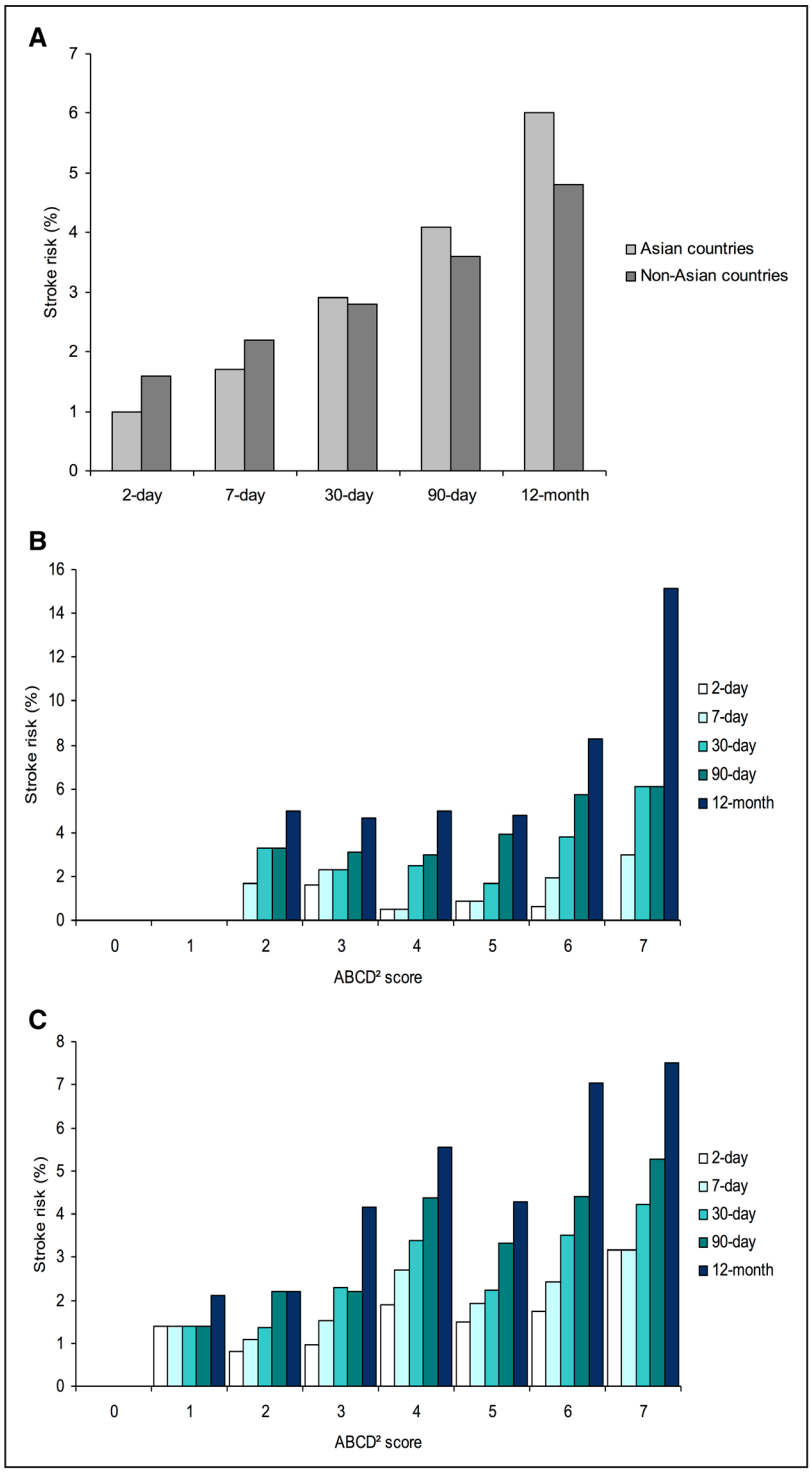

Figure 2. Short-term stroke rates in Asian and non-Asian patients (**A**) and according to ABCD^2 score in Asian (**B**) and non-Asian (**C**) patients.

baseline characteristics and interaction between Asians and non-Asians. Large-artery atherosclerosis was highly associated with an increased stroke risk in both populations. There was no regional interaction between the TOAST distribution and stroke risk ($P_{interaction}$=0.54). Coronary artery disease, regular alcohol consumption, and rural residency were more associated with stroke risk in Asians than in non-Asians ($P_{interaction}$=0.06, 0.05, and 0.03, respectively), whereas the reverse was true for extracranial stenosis ($P_{interaction}$=0.05). Multivariable analysis showed that multiple acute infarcts (P=0.005) and current alcohol consumption (P=0.02) were independent predictors of stroke recurrence in Asians (Table 4). In non-Asians, intracranial stenosis (P<0.001), ABCD^2 score (P<0.001), atrial fibrillation (P=0.008), extracranial stenosis (P=0.03), and previous stroke or TIA (P=0.03) were independent predictors. After handling missing data, selected predictors were similar in each group (Table VI in the online-only Data Supplement).

Table 4. Multivariable Analysis of Predictors of 1-Year Stroke in Asian and Non-Asian Patients

	HR (95% CI)	*P* Value
Asians		
Current alcohol consumption	2.08 (1.10–3.93)*	0.02
Acute infarct		0.002
No acute infarct	1.00 (ref)*	
Single acute infarct	1.00 (0.47–2.11)*	0.99
Multiple acute infarcts	2.85 (1.37–5.93)*	0.005
Living in rural area	2.43 (0.87–6.81)*	0.09
Non-Asians		
Intracranial stenosis	2.40 (1.45–3.97)†	<0.001
$ABCD^2$ score		<0.001
0–3	1.00 (ref)†	
4–5	2.02 (1.12–3.64)†	0.02
6–7	3.67 (1.90–7.09)†	<0.001
Atrial fibrillation/flutter	2.13 (1.21–3.73)†	0.008
Extracranial stenosis	1.74 (1.06–2.85)†	0.03
Stroke, transient ischemic attack	1.77 (1.06–2.94)†	0.03

CI indicates confidence interval; and HR, hazard ratio.

*Calculated from stepwise-selection Cox model based on 587 patients with nonmissing candidate variables.

†Calculated from stepwise-selection Cox model based on 1864 patients with nonmissing candidate variables.

Discussion

Among the Asian patients with a TIA or minor stroke, 80% of whom were evaluated within 24 hours of onset by a specialist, the 1-year stroke risk was only 6.0%. This was not statistically different from that in non-Asian patients and much lower than that reported in historical Western cohort studies.[11,12] The stroke risk at 2, 30, and 90 days of 1%, 3%, and 4% in our study were less than half that of 4%, 8%, and 9%, respectively, found in a meta-analysis of 11 observational studies published before 2006.[13] Our results may indicate that a wide range of care systems specific to TIA, including emergency department, stroke unit, and day clinic, are effective as long as patients are assessed and treated rapidly. Furthermore, our patients seemed to undergo rigorous risk factor managements during follow-up. Specifically, among Asian patients with 60% prevalence of hypertension, ≥1 antihypertensive agents were used in 56%. Likewise, among patients with 65% prevalence of dyslipidemia, ≥1 lipid-lowering agents were used in 64%. At 12-month, a mean blood pressure of 131/78 mm Hg and a mean low-density lipoprotein cholesterol level of 98 mg/dL were achieved. In addition, 68% of active smokers quit smoking. These interventions represent the standard of modern secondary prevention strategies recommended by the existing guideline,[14] and our risk estimates would correspond closely to the true contemporary residual risk.

The risk of recurrent TIA after a TIA or minor stroke in non-Asians was almost double that of Asians and was an unexpected finding. Nevertheless, recurrent TIA would not affect the patients' functional prognosis (ie, stroke-related disability). It remains to be further explored why only TIA and not stroke increased, given that they share risk factors in common. A higher proportion of negative diffusion-weighted imaging in non-Asians might be an explanation, possibly indicating that the viable tissue is still at higher risk of a subsequent TIA. However, this may contradict the fact that positive diffusion-weighted imaging is a strong predictor for future stroke.[15] Considering that TIA is a soft end point and the evaluation of recurrent TIA differed by site, further studies with more strict adjudication for recurrent TIA are warranted to confirm our results.

The risk of intracranial hemorrhage was not different between Asians and non-Asians (0.5% and 0.3%, respectively), despite that Asian people are generally at an almost twice higher risk of intracranial hemorrhage than non-Asians.[16] It was perhaps because of the short (1-year) follow-up that did not allow hemorrhagic stroke to accrue. There is a possibility that less aggressive antithrombotic therapy was selected for Asian patients, but our risk estimate of 0.5% was similar to that found in the CHANCE trial (0.5%; Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) in which dual antiplatelet therapy was administered in Chinese patients.[17] This may suggest that the hemorrhagic risk after a TIA or minor stroke (but not severe stroke) is comparatively low even in Asians. Rapidly controlled and well-controlled hypertension might also in part contribute to lower the risk and minimize racial disparities.

Although the predictive ability of $ABCD^2$ score was similar, the score may have less impact in stratifying low- to moderate-risk patients when applied to the current care settings in Asia. Presumably, as a consequence of the contemporary treatment approach, no recurrent stroke occurred in Asians in the lowest range of $ABCD^2$ score (0 and 1). Also, stroke risk for patients with an $ABCD^2$ score 2 to 5 were markedly and similarly reduced to <5% at 1 year and could not be stratified by $ABCD^2$ score. On the other hand, patients in the highest range of $ABCD^2$ score (6 and 7) remained at high residual risk (>10%). It should be noticed, however, that 19% of recurrent strokes occurred in patients with a low $ABCD^2$ score (<4), and 78% (7/9) of them could be signaled by the presence of at least one major investigational finding (acute infarct, ipsilateral stenosis >50%, and atrial fibrillation).

TIA in Asians was characterized by a higher $ABCD^2$ score, higher prevalence of intracranial stenosis and acute infarcts on neuroimaging, and a lower frequency of cortical symptoms. These features could be related to the difference in the distribution of TOAST subtype; large-artery atherosclerosis and small-vessel disease were more common in Asians, whereas cardioembolism was more common in non-Asians. Small-vessel disease was less frequently diagnosed in non-Asians because it might be difficult to affirm in cases with no visible infarcts on brain imaging. Large-artery atherosclerosis was associated with the highest risk of recurrent stroke in both populations. In particular, intracranial stenosis increased the stroke risk in non-Asians ($P<0.001$) and also in Asians by a marginal trend toward significance ($P=0.09$), which seems in line with the results from SOS-TIA study.[18] The elucidation of a better treatment strategy for this high-risk subgroup can be an important issue for global

health, given the massive population growth in Asia where intracranial stenosis is particularly prevalent.[19]

There were several differences in the predictors of stroke between Asian and non-Asian populations. Of note, regular alcohol consumption was potentially an important modifiable risk factor for Asians. Previous studies also reported the associations of excessive alcohol intake with stroke risk for Asian people.[20,21] Over recent decades, a marked increase in alcohol consumption and related harm has occurred in Asian countries, probably related to rapid industrial development and urbanization.[22,23] Our data suggest that prevention of excessive alcohol consumption can be one of the targets for a reduction in stroke risk after TIA in Asia and may have important implications for public health policy and education in this region.

Strengths and Limitations

A major strength of this study is that it included a large, prospective, multicenter, and multinational cohort. Case ascertainments were reliably done by stroke specialists with imaging-based assessments, and robust clinical and socioeconomic data were obtained using a standard protocol. Direct comparisons could be made between regions, in contrast to existing studies, which were mostly retrospective pooled analyses and limited by some difficulties because of a lack of standard settings, methods, or definitions across cohorts.

There are some important limitations, which are mainly related to the inherent nature of an observational study. Even after extensive adjustment, residual confounding cannot be ruled out. Because participating sites were not selected at random, the cohort could differ from those of the general TIA/stroke population. Another possible limitation is missing data; among 4583 initially included patients, 383 (8.4%) were lost to follow-up. Finally, it is important to note that there is still a heterogeneity even within Asian populations in terms of genetic background, behavioral and cultural diversities, and quality of stroke care, especially between economically developed and developing countries. In addition, we assumed residence in Asian countries as a surrogate for race/ethnicity without considering potential varieties of racial backgrounds (eg, Asian descendants in non-Asian countries, mixed races). In the TIAregistry.org, 99% of Asians originated from middle- to high-income countries in East Asia (China, Hong Kong, Japan, Korea, and Taiwan). Although they share relatively common genetic, cultural, and socioeconomic backgrounds, our results cannot be generalizable to the whole Asian populations.

Conclusions

Urgent intervention in dedicated units by stroke specialists contributes to a low vascular risk in Asian and in non-Asian patients with TIA or minor ischemic stroke. However, substantial racial–ethnic or regional differences exist in various clinical and investigational parameters and their impacts on the risk of stroke. Our data will help develop population-specific stroke prevention strategies and plan for appropriate allocation of resources for care of TIA patients. In addition, the study raises challenging issues on how to reduce the residual risk even after the current optimal treatment guidelines are followed.

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Disclosures

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Differences in Characteristics and Outcomes Between Asian and Non-Asian Patients in the TIAregistry.org

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Figure I. Flow-chart of the study

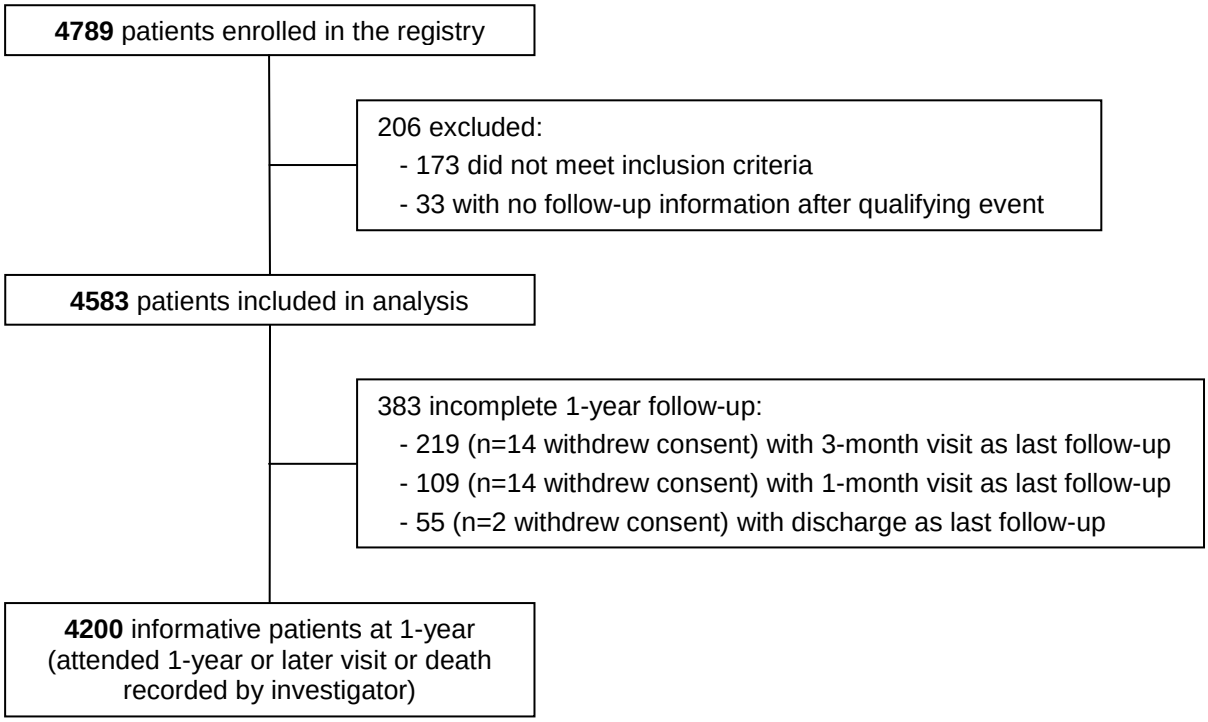


Table I. Characteristics of first contact and setting in Asian and non-Asian patients

	Non-Asian n=3513	Asian n=1070	p-value*
Time to first contact (hour)†			<0.001
<12	1920 (81.3)	510 (68.2)	
12 – 24	207 (8.8)	122 (16.3)	
24 – 48	125 (5.3)	63 (8.4)	
48 – 96	83 (3.5)	34 (4.5)	
96 – 168	26 (1.1)	19 (2.5)	
Type of first contact			<0.001
Emergency physician	1387 (39.5)	586 (54.8)	
Primary care physician	1031 (29.3)	160 (14.9)	
Neurologist	409 (11.6)	156 (14.6)	
Pre-hospitalization paramedics	374 (10.6)	36 (3.4)	
Direct presentation to the TIA clinic	74 (2.1)	61 (5.7)	
Other or unknown	238 (6.8)	71 (6.6)	
Type of setting			<0.001
Emergency department	925 (26.3)	631 (58.9)	
Stroke unit	1642 (46.7)	321 (30.0)	
Day clinic	712 (20.3)	35 (3.3)	
Outpatient clinic	234 (6.7)	83 (7.8)	

Data are number (%).
Abbreviation: TIA=transient ischemic attack
* Adjusted by age and sex
† Time from symptom onset to call to any medical attention. Data were available for 3109 (2361 non-Asian and 748 Asian) patients.

Table II. Pre-admission medications and treatments at discharge in Asian and non-Asian patients

	Prior admission		At discharge	
	Non-Asian n=3513	**Asian n=1070**	**Non-Asian n=3513**	**Asian n=1070**
≥1 antiplatelet agent	1047 (30.0)	178 (16.8)†	3130 (90.0)	916 (90.8)
Aspirin	929 (26.6)	140 (13.2)†	2408 (70.1)	607 (60.5)†
Other antiplatelet agent	216 (6.2)	56 (5.3)	1073 (31.2)	469 (46.8)†
Aspirin and other antiplatelet agent	101 (2.9)	20 (1.9)	418 (12.2)	175 (17.4)†
≥1 anticoagulant agent	194 (5.5)	36 (3.4)‡	565 (16.4)	226 (21.5)†
≥1 antihypertensive agent	2026 (57.8)	469 (44.2)†	2475 (71.1)	600 (56.0)†
1 agent	814 (23.3)	234 (22.4)†	1079 (31.6)	337 (33.0)†
2 agents	664(19.0)	138 (13.2)	779 (22.8)	125 (12.2)
3 or more agents	529 (15.1)	70 (6.7)	546 (15.9)	64 (6.3)
≥1 lipid-lowering agent	1059 (30.3)	154 (14.5)†	2486 (71.5)	680 (64.3)†
Statin	988 (28.2)	137 (13.0)†	2395 (69.6)	627 (59.7)†
Other lipid-lowering agent	108 (3.1)	17 (1.6)‡	100 (4.1)	51 (7.6)†
Quit smoking*	-	-	401 (67.7)	173(68.4)
Counseled health care professional*	-	-	248 (62.5)	105(62.5)
≥1 smoking cessation drug*	-	-	105(26.4)	0(0.0)
Carotid revascularization	-	-	156 (4.4)	11 (1.0)†
Endarterectomy	-	-	122 (3.5)	4 (0.4)‡
Stenting or angioplasty	-	-	34 (1.0)	7 (0.6)
Intracranial revascularization	-	-	9 (0.3)	2 (0.2)

Data are number (%) unless otherwise indicated.
* Among current smokers
† Age- and sex-adjusted p <0.0005
‡ Age- and sex-adjusted p <0.05

Table III. Self-reported medications and examinations at 3 months and 12 months in Asian and non-Asian patients

	3-month		12-month	
	Non-Asian n=3105	**Asian n=982**	**Non-Asian n=3049**	**Asian n=931**
≥1 antiplatelet agent	2514 (81.9)	779 (79.9)	2347 (79.6)	705 (76.3)
Aspirin	1949 (63.6)	496 (53.3)†	1775 (60.3)	464 (50.4)†
Other antiplatelet agent	928 (30.3)	346 (37.2)†	166 (5.6)	129 (14.0)†
Aspirin and other antiplatelet agent	365 (11.9)	108 (11.6)	266 (9.0)	70 (7.6)
≥1 anticoagulant agent	541 (17.7)	132 (13.6)‡	543 (18.5)	129 (14.0)‡
≥1 antihypertensive agent	2260 (73.8)	519 (54.9)†	2161 (74.1)	578 (62.8)†
1 agent	906 (40.1)	304 (58.6)†	827 (28.4)	320 (34.9)†
2 agents	722 (31.9)	151(29.1)	733 (25.2)	187 (20.4)†
3 or more agents	626 (27.7)	59 (11.4)	593 (20.4)	69 (7.5)†
≥1 lipid-lowering agent	2219 (72.4)	578 (61.3)†	2060 (70.7)	531 (57.4)†
Statin	2169 (70.9)	538 (57.4)†	2008 (69.0)	488 (52.9)†
Other lipid-lowering agent	85 (2.8)	42 (4.5)†	100 (3.4)	44 (4.8)‡
Systolic BP, mean (SD), mm Hg	134 (18)	133 (17)	134 (17)	131 (15)†
Diastolic BP, mean (SD), mm Hg	77 (11)	78 (11)	77 (10)	78 (11)
Total cholesterol, mean (SD), mg/dl	173 (44)	175 (36)	172 (40)	175 (35)
LDL-cholesterol, mean (SD), mg/dl	95 (36)	99 (30)	94 (36)	98 (28)
HDL-cholesterol, mean (SD), mg/dl	54 (18)	53 (14)	55 (17)	51 (15)†
Triglyceride, median (IQR), mg/dl*	108 (82-156)	115 (82-155)	107 (77-151)	117 (88-116)†
HDL-c ≤40 mg/dl and Triglycerides ≥150 mg/dl	78 (2.2)	39 (3.6)‡	100 (2.8)	66 (6.2)†
HDL-c ≤35 mg/dl and Triglycerides ≥200 mg/dl	32 (0.9)	4 (0.4)	41 (1.2)	18 (1.7)

Abbreviations: BP=blood pressure; IQR=interquartile range; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SD=standard deviation

* Analyzed using the logarithmic values

† Age- and sex-adjusted p <0.0005

‡ Age- and sex-adjusted p <0.05

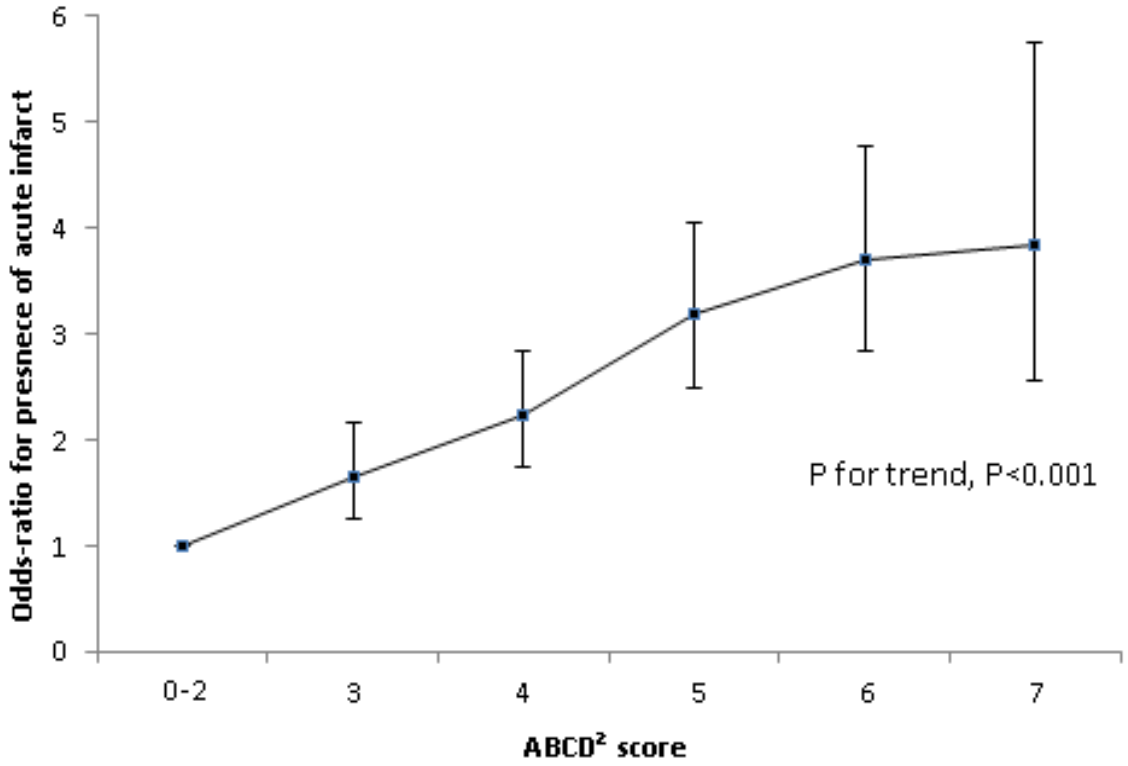
Table IV. Stroke risk at 3 months and 12 months according to ABCD² score in Asian patients with and without acute infarct

	3-month				12-month			
	With acute infarct		Without acute infarct		With acute infarct		Without acute infarct	
ABCD² score	n/N	% risk* (95% CI)	n/N	% risk* (95% CI)	n/N	% risk* (95% CI)	n/N	% risk* (95% CI)
0-2	5/111	4.5 (1.9-10.5)	7/530	1.3 (0.6-2.8)	5/111	4.5 (1.9-10.5)	9/530	1.7(0.9-3.3)
3	6/168	3.6 (1.6-1.8)	13/485	2.7 (1.6-4.6)	9/168	5.4 (2.9-10.2)	18/484	3.8 (2.4-6.0)
4	16/301	5.4 (3.3-8.6)	22/645	3.4 (2.3-5.2)	21/301	7.1 (4.7-10.7)	29/645	4.6 (3.2-6.6)
5	13/362	3.7 (2.1-6.2)	18/543	3.3 (2.1-5.3)	17/362	4.8 (3.0-7.7)	22/543	4.1 (2.7-6.2)
6	19/269	7.1 (4.6-10.9)	10/348	2.9 (1.6-5.3)	26/269	9.8 (6.8-14.1)	18/348	5.4 (3.5-8.5)
7	4/57	7.0 (2.7-17.6)	3/71	4.2 (1.4-12.5)	5/57	8.8 (3.8-19.9)	7/71	10.1 (5.0-20.1)

Abbreviations: CI=confidence interval

* Kaplan-Meier estimate

Figure II. ABCD² score and presence of acute infarct in Asian patients



Odds ratios with 95% confidence intervals relative to an ABCD^2 score of 0-2 are shown.

Table V. Age- and sex-adjusted hazard ratio of baseline characteristics to stroke risk and interaction between Asian and non-Asian patients

	Non-Asian		Asian		
	Age- and sex-adjusted HR (95% CI)	p-value	Age- and sex-adjusted HR (95% CI)	p-value	Interaction p-value*
Demographics					
Age, (per 10 years)	1.18 (1.04-1.34)	0.01	1.31 (1.05-1.63)	0.02	0.43
Men	1.35 (0.97-1.89)	0.08	1.57 (0.87-2.82)	0.13	0.77
Medical history					
Hypertension	1.17 (0.82-1.65)	0.39	1.19 (0.69-2.05)	0.52	0.91
Diabetes	1.35 (0.94-1.95)	0.10	1.27 (0.72-2.26)	0.41	0.85
Dyslipidemia	1.09 (0.76-1.56)	0.65	0.95 (0.56-1.61)	0.85	0.68
Former smokers	0.74 (0.50-1.08)	0.12	0.67 (0.33-1.33)	0.25	0.81
Current smokers	1.22 (0.81-1.84)	0.35	1.54 (0.84-2.82)	0.16	0.53
Regular alcohol consumption	1.09 (0.74-1.61)	0.66	2.13 (1.22-3.72)	0.003	0.05
Regular physical activity	0.89 (0.59-1.33)	0.56	1.04 (0.57-1.88)	0.90	0.67
Stroke, transient ischemic attack	1.64 (1.15-2.35)	0.007	1.30 (0.74-2.31)	0.36	0.50
Coronary artery disease	0.80 (0.50-1.29)	0.36	1.81 (0.91-3.62)	0.09	0.06
Peripheral artery disease	0.82 (0.34-2.02)	0.67	1.21 (0.17-8.78)	0.84	0.73
Atrial fibrillation/flutter	1.34 (0.84-2.13)	0.22	0.97 (0.35-2.69)	0.95	0.57
Congestive heart failure	0.95 (0.39-2.32)	0.91	1.71 (0.41-7.10)	0.46	0.49
Living and socioeconomics indicators					
Living alone	0.83 (0.59-1.16)	0.27	1.04 (0.58-1.89)	0.88	0.50
Living in rural area	0.94 (0.61-1.45)	0.77	2.61 (1.18-5.75)	0.02	0.03
Unemployment†	0.88 (0.35-2.19)	0.79	1.82 (0.69-4.76)	0.22	0.33
Educational level		0.24		0.55	0.52
None	1.00 (ref)		1.00 (ref)		
Primary	1.00 (0.49-2.01)	1.00	0.55 (0.21-1.49)	0.24	
Secondary	0.68 (0.33-1.40)	0.30	0.67 (0.28-1.59)	0.36	
Tertiary	0.88 (0.40-1.92)	0.75	0.88 (0.34-2.32)	0.80	
Examinations					
Body mass index, (per 5 kg/m²)	0.80 (0.65-0.99)	0.04	1.05 (0.76-1.46)	0.75	0.23
Atherogenic dyslipidemia	1.05 (0.64-1.73)	0.83	1.04 (0.51-2.12)	0.92	0.94
TOAST classification		0.001		0.04	0.54
Large artery atherosclerosis	2.36 (1.55-3.59)	<0.001	4.59 (1.39-15.10)	0.01	
Small vessel disease	1.27 (0.78-2.06)	0.33	2.41 (0.70-8.33)	0.16	
Cardioembolism	1.43 (0.87-2.36)	0.16	2.84 (0.70-11.42)	0.14	
Other determined cause	1.31 (0.61-2.81)	0.49	6.01 (1.34-26.97)	0.02	
Undetermined	1.00 (ref)		1.00 (ref)		
ABCD² score		0.02		0.16	0.66
0-3	1.00 (ref)		1.00 (ref)		
4-5	1.50 (0.97-2.31)	0.07	1.04 (0.47-2.32)	0.92	
6-7	2.05 (1.26-3.35)	0.004	1.88 (0.80-4.42)	0.15	
Major investigational findings					
Acute infarct		<0.001		<0.001	0.31
No acute infarct	1.00 (ref)		1.00 (ref)		
Single acute infarct	1.85 (1.27-2.70)	0.001	1.20 (0.61-2.35)	0.60	
Multiple acute infarcts	3.02 (2.01-4.54)	<0.001	3.81 (2.02-7.16)	<0.001	
≥1 intracranial stenosis ≥50% or occlusion	2.41 (1.61-3.59)	<0.001	1.64 (0.92-2.93)	0.09	0.28
≥1 extracranial stenosis ≥50% or occlusion	2.40 (1.68-3.42)	<0.001	1.08 (0.54-2.18)	0.82	0.05
Atrial fibrillation	1.55 (1.00-2.40)	0.05	1.64 (0.79-3.41)	0.18	0.91

Abbreviations: CI=confidence interval; HR=hazard ratio

* P-value for interaction between Asian and non-Asian patients

† Excluding student, social pensioner on disability grant, and old age pensioner

Table VI. Multivariable analysis of predictors of one-year stroke in Asian and non-Asian patients after handling missing data

Asian	**HR (95% CI)**	**p-value**
Current alcohol consumption	2.16 (1.20-3.90)	0.01
Live in rural area	2.74 (1.22-6.23)	0.01
Acute infarct		
No acute infarct	1.00 (ref)	-
Single acute infarct	1.14 (0.54-2.39)	0.73
Multiple acute infarcts	2.83 (1.40-5.81)	0.004
Coronary artery disease	2.20 (1.07-4.48)	0.03
TOAST classification		
Large artery atherosclerosis	4.48 (1.34-15.03)	0.01
Small vessel disease	3.03 (0.86-10.70)	0.08
Cardioembolism	2.89 (0.68-12.18)	0.15
Other determined cause	7.84 (1.73-36.23)	0.008
Undetermined cause	1.00 (ref)	-
Non-Asian	**HR (95% CI)**	**p-value**
ABCD² score		
0-3	1.00 (ref)	-
4-5	1.42 (0.92-2.20)	0.11
6-7	1.84 (1.13-3.00)	0.01
Extracranial stenosis	1.97 (1.36-2.83)	<0.001
Stroke, transient ischemic attack	1.62 (1.13-2.32)	0.008
Acute infarct		
No acute infarct	1.00 (ref)	-
Single acute infarct	1.57 (1.03-2.36)	0.03
Multiple acute infarcts	2.22 (1.43-3.42)	<0.001
Intracranial stenosis	1.68 (1.08-2.59)	0.02
Atrial fibrillation	1.49 (0.96-2.29)	0.07

Abbreviations: CI=confidence interval; HR=hazard ratio