

ABCD3 and ABCD3-I Scores Are Superior to ABCD2 Score in the Prediction of Short- and Long-Term Risks of Stroke After Transient Ischemic Attack

Takuya Kiyohara, MD; Masahiro Kamouchi, MD; Yasuhiro Kumai, MD; Toshiharu Ninomiya, MD; Jun Hata, MD; Sohei Yoshimura, MD; Tetsuro Ago, MD; Yasushi Okada, MD; Takanari Kitazono, MD; for the FSR investigators

Background and Purpose—Several risk scores have been developed to predict the stroke risk after transient ischemic attack (TIA). However, the validation of these scores in different cohorts is still limited. The objective of this study was to elucidate whether these scores were able to predict short-term and long-term risks of stroke in patients with TIA.

Methods—From the Fukuoka Stroke Registry, 693 patients with TIA were followed up for 3 years. Multivariable-adjusted Cox proportional hazards model was used to assess the hazard ratio of risk factors for stroke. The discriminatory ability of each risk score for incident stroke was estimated by using *C*-statistics and continuous net reclassification improvement.

Results—The multivariable-adjusted Cox proportional hazards model revealed that dual TIA and carotid stenosis were both significant predictors for stroke after TIA, whereas abnormal diffusion-weighted image was not. ABCD3 (*C*-statistics 0.61) and ABCD3-I (*C*-statistics 0.66) scores improved the short-term predictive ability for stroke (at 7 days) compared with the ABCD2 score (*C*-statistics 0.54). Addition of intracranial arterial stenosis (at 3 years, continuous net reclassification improvement 30.5%; $P < 0.01$) and exclusion of abnormal diffusion-weighted imaging (at 3 years, continuous net reclassification improvement 24.0%; $P < 0.05$) further improved the predictive ability for stroke risk until 3 years after TIA.

Conclusions—The present study demonstrates that ABCD3 and ABCD3-I scores are superior to the ABCD2 score for the prediction of subsequent stroke in patients with TIA. Addition of neuroimaging in the ABCD3 score may enable prediction of long-term stroke risk after TIA. (*Stroke*. 2014;45:418-425.)

Key Words: ABCD2 score ■ prognosis ■ stroke ■ transient ischemic attack

In patients with transient ischemic attack (TIA), subsequent stroke often occurs early after the first symptoms.^{1,2} Therefore, early diagnosis and prompt treatment are required to prevent subsequent stroke in patients presenting with TIA.^{3,4}

To predict early occurrence of stroke after TIA, several risk scores have been developed and widely used in clinical practice. In 2005, the ABCD score was developed by Rothwell et al⁵ to predict the risk of stroke after TIA; the original ABCD score consisted of 4 components, namely, age, blood pressure, clinical features of TIA, and duration of symptoms. In 2007, Johnston et al⁶ proposed a new risk score, ABCD2, in which the presence of diabetes mellitus was added as another component to the original ABCD score. In 2010, Merwick et al⁷ proposed 2 novel scores to predict early risk of stroke after TIA, namely, the ABCD3 and ABCD3-I scores. In the ABCD3 score, dual TIA (the presence of ≥ 2 TIA symptoms within 7 days) is added to the ABCD2 score. In the ABCD3-I score, the presence of abnormal findings

on neuroimaging (ie, carotid stenosis or abnormal acute diffusion-weighted image [DWI] on brain magnetic resonance imaging [MRI]) was further added to the ABCD3 score.⁷ Moreover, recent studies have shown that intracranial arterial stenosis was associated with recurrent stroke after TIA.^{8,9} Although the predictive abilities of ABCD and ABCD2 have been investigated by many studies, the results are still conflicting.¹⁰⁻¹⁸ Moreover, those of the ABCD3 and ABCD3-I scores have not yet been validated, and the ability of these scores to predict stroke after TIA over the long term is unknown.

The aims of the present study were to elucidate whether the ABCD2, ABCD3, and ABCD3-I scores, with or without addition of intracranial arterial stenosis, are associated with short-term and long-term risks of stroke after TIA, and to determine whether the ABCD3 and ABCD3-I scores are superior to the ABCD2 score for the prediction of stroke after TIA, using the data from a prospective multicenter study in Japan.

Received August 7, 2013; accepted October 29, 2013.

From the Departments of Medicine and Clinical Science (T. Kiyohara, Y.K., T.N., J.H., S.Y., T.A., T. Kitazono), Health Care Administration and Management (M.K.), and Environmental Medicine (T.N., J.H.), Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Nephrology, Hypertension, and Stroke, Kyushu University Hospital, Fukuoka, Japan (M.K., T.A., T. Kitazono); Department of Cerebrovascular Disease and Neurology, Hakujyujii Hospital, Fukuoka, Japan (Y.K.); Department of Cerebrovascular Medicine, Fukuoka Red Cross Hospital, Fukuoka, Japan (S.Y.); and Department of Cerebrovascular Medicine, Cerebrovascular Center and Clinical Research Institute, National Kyushu Medical Center, Fukuoka, Japan (Y.O.).

Correspondence to Masahiro Kamouchi, MD, Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: kamouchi@hcam.med.kyushu-u.ac.jp

© 2013 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.113.003077

Methods

Study Population

The Fukuoka Stroke Registry (FSR) is a multicenter, hospital-based database of patients with acute stroke or TIA, and 7 stroke centers in Fukuoka, Japan, participate in the registry (see Appendix).^{19,20} From June 2007 to August 2012, a total of 6246 patients with acute stroke or TIA who were hospitalized within 7 days after onset were registered in the FSR database. In the present study, 693 patients with definite TIA who did not receive thrombolytic therapy were analyzed.

TIA was defined as a focal cerebral ischemic event with neurological symptoms lasting <24 hours regardless of brain lesions detected by brain imaging tests, including computed tomography (CT) and MRI, and was diagnosed on admission by >1 stroke neurologist in the hospital. Patients received antiplatelet or anticoagulant therapy depending on the pathogenesis of TIA. Treatments for risk factors were performed based on the Japanese guidelines for the management of stroke. The medical information was collected using a case report form and medical record and inserted into the database with an aid of expert research nurses.

Risk Factors

Blood pressure was measured in the chronic stage after TIA, and hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a previous history of hypertension. Diabetes mellitus was determined either by the diagnostic criteria of the Japan Diabetes Society²¹ in the chronic stage or a medical history of diabetes mellitus. Dyslipidemia was defined as either a serum low-density lipoprotein-cholesterol ≥ 3.26 mmol/L, high-density lipoprotein-cholesterol < 1.03 mmol/L, triglycerides ≥ 1.69 mmol/L, or a history of antihyperlipidemic medication. Atrial fibrillation was diagnosed based on electrocardiographic findings on admission or during hospitalization, or a previous history of atrial fibrillation. Estimated glomerular filtration rate (eGFR) was determined using the equation proposed by the Japanese Society of Nephrology as follows: $eGFR$ (mL/min per 1.73 m²) = $194 \times (\text{serum creatinine [mg/dL]})^{-1.094} \times (\text{age [year]})^{-0.287} \times 0.739$ (if female).²² Chronic kidney disease was defined as a low eGFR (< 60 mL/min per 1.73 m²). Smoking was defined as a previous or current smoking habit before the onset of TIA. Coronary heart disease was defined as a previous history of angina pectoris, myocardial infarction, and percutaneous coronary intervention or coronary artery bypass graft

surgery. Dual TIA was defined as the occurrence of ≥ 2 TIAs (ie, the index TIA and one other TIA) within 7 days.

Neuroimaging Findings

Carotid stenosis was defined as $> 50\%$ narrowing in the lumen of the internal carotid artery, which was responsible for the neurological symptoms detected by carotid ultrasonography, magnetic resonance angiography (MRA), CT angiography (CTA), or conventional angiographic examination. Intracranial arterial stenosis was defined as $> 50\%$ narrowing in the lumen of the arteries, which were responsible for the neurological symptoms detected by intracranial MRA, CTA, or angiography. The presence of these vascular lesions was evaluated by carotid ultrasonography in 660 patients (95.2%), intracranial MRA in 672 patients (97.0%), extracranial MRA in 254 patients (37.0%), CTA in 158 patients (22.8%), and conventional angiography in 57 patients (8.2%).

CT imaging was performed in 402 patients (58.0%) predominantly to exclude hemorrhagic stroke or evaluation for arterial lesions. DWI findings on MRI on admission or during hospitalization were considered abnormal if there was ≥ 1 hyperintense area that was consistent with the presence of an infarcted lesion. The abnormal DWI findings were diagnosed by stroke neurologists and neuroradiologists. DWI on brain MRI was performed in 675 patients (97.4%). Among them, 345 patients underwent MRI within 24 hours of the TIA symptoms, and 615 patients underwent MRI within 3 days. For 18 patients, MRI was not performed because of contraindications, including 15 pacemaker implantations, 1 aorta stent, 1 cerebral artery clip, and 1 patient with claustrophobia.

Risk Assessment of Stroke Events

The risk assessment of subsequent stroke events for individual patients was performed by means of ABCD2, ABCD3, and ABCD3-I scores in the same manner as in the previous studies.⁵⁻⁷ We modified the original ABCD3-I score based on the findings from the multivariable analyses in this study. We constituted new scores with a combination of DWI abnormalities (d), and carotid stenosis or $\geq 50\%$ stenosis of intracranial arterial stenosis (c/i; Table 1). The ABCD3-I(d,c/i) score was designated by adding an intracranial artery to original ABCD3-I, and the ABCD3-I(c/i) score was defined as the ABCD3-I(d,c/i) score with the abnormal DWI excluded (Table 1).

Table 1. Point Score of ABCD2, ABCD3, and ABCD3-I Scores

	ABCD2 Score	ABCD3 Score	ABCD3-I Score	ABCD3-I(d, c/i) Score	ABCD3-I(c/i) Score
Age ≥ 60 y	1	1	1	1	1
Blood pressure $\geq 140/90$ mmHg	1	1	1	1	1
Clinical features					
Speech impairment without weakness	1	1	1	1	1
Unilateral weakness	2	2	2	2	2
Duration, min					
10–59	1	1	1	1	1
≥ 60	2	2	2	2	2
Diabetes mellitus present	1	1	1	1	1
Dual TIA	NA	2	2	2	2
Imaging					
Ipsilateral $\geq 50\%$ stenosis of internal carotid artery	NA	NA	2	NA	NA
Ipsilateral $\geq 50\%$ stenosis of internal carotid artery and/or cerebral major artery	NA	NA	NA	2	2
Acute diffusion-weighted imaging hyperintensity	NA	NA	2	2	NA
Total	0–7	0–9	0–13	0–13	0–11

Dual transient ischemic attack (TIA) was defined as TIA prompting medical attention plus at least one other TIA in the preceding 7 days. (c) indicates carotid stenosis; (d), diffusion-weighted image; (i), intracranial arterial stenosis; and NA, not applicable.

Stroke Occurrence

The main outcome of this study was a stroke (either ischemic or hemorrhagic) after TIA. Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. Stroke events were identified by trained research nurses who were blinded to the clinical data through telephone interviews using a standardized interview form. Patients were followed up at 3, 6, and 12 months after onset, and yearly thereafter. All information was reviewed by the event committee members, who were masked to the clinical background. When the committee members could not be convinced of stroke event, detailed information on subsequent stroke was also sought from general practitioners or hospital records. All patients were followed up prospectively during hospitalization and after discharge for a median of 392 days. During the follow-up period, 113 subjects experienced subsequent stroke events.

Statistical Analysis

The incidence of stroke after TIA was calculated by the Kaplan–Meier method and compared by using a Cox proportional hazards model. The hazard ratios (HRs) and their 95% confidence intervals (CIs) for the development of stroke at 7 days, 90 days, and 3 years after TIA were estimated by using a multivariable-adjusted Cox proportional hazards model. We constituted multivariable models that included factors of ABCD2, ABCD3, and ABCD3-I scores, and/or intracranial arterial stenosis. To assess the accuracy of the risk assessment of incident stroke for each risk score, C-statistics were calculated, and the difference in the C-statistics were tested using the DeLong method.²³ To investigate the extent to which each risk score improved the risk assessment of incident stroke in comparison with the ABCD2 score, the continuous net reclassification improvement (NRI) was calculated,²⁴ with the predicted probabilities of incident stroke being determined for each participant using the relevant Cox model. Statistical analyses were performed using the JMP version 9 software program (SAS Institute Inc, Cary, NC). Two-sided values of $P < 0.05$ were considered statistically significant in all analyses.

Ethical Considerations

The ethics committee of each hospital approved this study. Written informed consent was obtained from all participants.

Results

Demographics of the Patients

Table 2 shows the characteristics of the 693 patients. The distribution of the patients is shown according to the scores in Table 2. Antithrombotics had been administered in 243 patients before onset (antiplatelets in 210 patients, anticoagulants in 50 patients, and both in 17 patients). At discharge, antithrombotics were prescribed in 687 patients. Carotid endarterectomy and carotid artery stenting were performed during hospitalization in 20 and 7 patients, respectively.

Validity of ABCD2, ABCD3, and ABCD3-I Scores

The overall incidence of stroke was 6.9% at 7 days, 10.4% at 90 days, and 21.6% at 3 years after onset of TIA. During the follow-up period, 38 patients died in this cohort. The Figure shows the incidence of stroke during the 3 years after TIA in patients with ABCD2, ABCD3, and ABCD3-I scores. When stratified by the ABCD2 score, the stroke incidence was significantly higher at 90 days and 3 years after TIA in the high-risk group than in the low-risk group (Figure A). When analyzed using the ABCD3 score, the stroke risk at each time point during the 3 years after TIA was significantly higher in the moderate- and high-risk groups than in the low-risk group (Figure B). When stratified by the ABCD3-I score, the risk of subsequent stroke was higher in the high-risk group than in the low- and moderate-risk groups (Figure C).

Table 2. Patient Characteristics

Age, y, mean±SD	69±13
Male, n/N (%)	431/693 (62.2)
Risk factors, n/N (%)	
Hypertension	525/693 (75.8)
Dyslipidemia	389/692 (56.2)
Diabetes mellitus	163/693 (23.5)
Atrial fibrillation	127/693 (18.3)
Smoking	376/693 (54.3)
Chronic kidney disease, n/N (%)	224/693 (32.3)
Coronary heart disease, n/N (%)	122/693 (17.6)
Previous stroke, n/N (%)	141/693 (20.3)
Clinical features, n/N (%)	
Speech impairment without weakness	78/693 (11.2)
Unilateral weakness	411/693 (59.3)
Duration of symptoms, min	
10–59	248/693 (35.8)
≥60	302/693 (43.6)
Dual TIA	132/693 (19.0)
Carotid stenosis, n/N (%)	151/693 (21.8)
Intracranial arterial stenosis, n/N (%)	154/689 (22.4)
Carotid and/or intracranial arterial stenosis, n/N (%)	264/693 (38.1)
Abnormal DWI, n/N (%)	285/675 (42.2)
Treatments, n/N (%)	
Antiplatelets	
Before onset	210/693 (30.3)
At discharge	569/693 (82.1)
Anticoagulants	
Before onset	50/693 (7.2)
At discharge	164/693 (23.7)
CEA or carotid artery stenting	27/693 (3.9)
ABCD2 score, median (interquartile range)	4 (3–5)
0–3:Low, n/N (%)	189/693 (27.2)
4–5:Moderate, n/N (%)	347/693 (50.0)
6–7:High, n/N (%)	157/693 (22.7)
ABCD3 score, median (interquartile range)	5 (4–6)
0–3:Low, n/N (%)	158/693 (22.8)
4–5:Moderate, n/N (%)	304/693 (43.9)
6–9:High, n/N (%)	231/693 (33.3)
ABCD3-I score, median (interquartile range)	6 (4–8)
0–3:Low, n/N (%)	93/675 (13.8)
4–7:Moderate, n/N (%)	407/675 (60.0)
8–13:High, n/N (%)	182/675 (25.9)

Dual transient ischemic attack (TIA) was defined as TIA prompting medical attention plus at least one other TIA in the preceding 7 days. CEA indicates carotid endarterectomy; and DWI, diffusion-weighted image.

Components of the ABCD3-I Scores and Risk of Stroke After TIA

Table 3 shows the results of a Cox proportional hazard model analysis performed to elucidate risk factors associated with stroke incidence in the short and long terms. In multivariable model 1, dual TIA, DWI abnormalities (d), and carotid stenosis

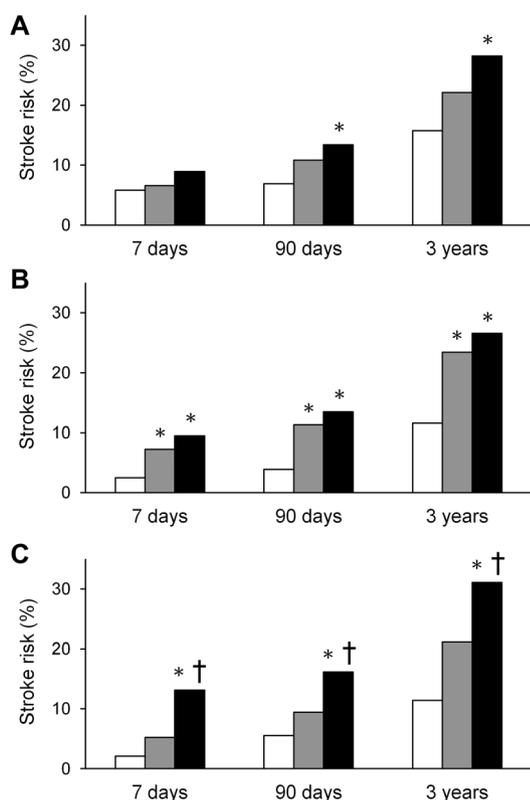


Figure. Stroke incidence after transient ischemic attack (TIA). The incidence of stroke at different time points after TIA is shown according to the risk categories of ABCD2 score (A), ABCD3 score (B), and ABCD3-I score (C). The different columns indicate stroke incidence in low-risk (open column), moderate-risk (shaded column), and high-risk patients (closed column). * $P < 0.05$ vs low-risk patients; † $P < 0.05$ vs moderate-risk patients.

(c) were included in addition to variables in the ABCD2 score. In model 2, carotid and/or intracranial arterial stenoses (c/i) were included instead of carotid stenosis as in model 1. As shown in model 1, carotid stenosis was a significant risk factor for stroke at each time point from 7 days to 3 years after TIA.

As shown in model 2, dual TIA and the combined carotid and/or intracranial arterial stenoses were significant risk factors for stroke at each time point during the 3 years after TIA. HRs for these factors in the short term tended to be higher than those in the long term. On the contrary, abnormal DWI was not a significant risk factor for stroke in either model. Based on these findings, we constituted ABCD3-I(d,c/i) and ABCD3-I(c/i) scores with a modification of the original ABCD3-I score (Table 1).

Comparisons of Predictive Abilities Among Several Risk Scores

C-statistics of the ABCD3, ABCD3-I, and ABCD3-I(d,c/i) scores were significantly higher than those of the ABCD2 score at 7 days, but not at 90 days and 3 years (Table 4). On the contrary, the C-statistics of ABCD3-I(c/i) showed significantly greater values than those of the ABCD2 score at all time points tested between 7 days and 3 years. The analyses using continuous NRI revealed that the ABCD3-I(d,c/i) and ABCD3-I(c/i) scores improved the risk classification of stroke events for 3 years after TIA (Table 5).

Discussion

The major findings of this study were the following: (1) the ABCD3 and ABCD3-I scores were superior to the ABCD2 score for predicting subsequent stroke in patients with definite TIA; (2) the inclusion of neuroimaging findings in the scoring improved the predictive ability for not only short-term, but also long-term occurrence of stroke after TIA; and (3) dual TIA and stenotic vascular lesions were significant predictors for stroke, whereas abnormal DWI was not.

Predictivity of the ABCD2 Score

The ABCD and ABCD2 scores were first developed to triage patients with high risk for stroke among those who were likely to have TIA diagnosed by a primary care physician. Some studies have indicated that the ABCD2 score is useful for predicting stroke after TIA,^{6,7,10-12} whereas other studies

Table 3. Multivariable-Adjusted Hazard Ratios for Stroke After TIA at Different Time Points of Follow-Up

Variables	7 Days		90 Days		3 Years		
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	
Model 1							
ABCD2, moderate (4–5)	(vs ABCD2, low)	1.04 (0.52, 2.22)	0.92	1.49 (0.81, 2.93)	0.20	1.32 (0.82, 2.19)	0.26
ABCD2, high (6–7)	(vs ABCD2, low)	1.81 (0.83, 4.10)	0.14	2.13 (1.07, 4.39)	0.03	1.92 (1.12, 3.32)	0.02
Dual TIA	(yes vs no)	2.88 (1.58, 5.13)	<0.001	2.06 (1.21, 3.38)	0.009	1.80 (1.17, 2.71)	0.008
Abnormal DWI	(yes vs no)	1.55 (0.88, 2.74)	0.13	1.09 (0.68, 1.74)	0.72	1.20 (0.82, 1.73)	0.34
Carotid stenosis	(yes vs no)	2.22 (1.23, 3.91)	0.009	1.73 (1.04, 2.82)	0.04	1.77 (1.17, 2.62)	0.007
Model 2							
ABCD2, moderate (4–5)	(vs ABCD2, low)	1.00 (0.50, 2.15)	0.99	1.45 (0.79, 2.84)	0.24	1.30 (0.81, 2.15)	0.29
ABCD2, high (6–7)	(vs ABCD2, low)	1.91 (0.87, 4.33)	0.11	2.16 (1.09, 4.46)	0.03	1.95 (1.14, 3.37)	0.01
Dual TIA	(yes vs no)	2.81 (1.54, 5.04)	0.001	2.01 (1.18, 3.32)	0.01	1.77 (1.14, 2.66)	0.01
Abnormal DWI	(yes vs no)	1.45 (0.82, 2.57)	0.20	1.04 (0.64, 1.66)	0.88	1.15 (0.79, 1.66)	0.47
Carotid stenosis and/or intracranial arterial stenosis	(yes vs no)	2.43 (1.37, 4.41)	0.002	1.95 (1.22, 3.15)	0.005	1.62 (1.11, 2.35)	0.01

Hazard ratio (HR) in moderate- or high-risk ABCD2 scores was compared with that in low-risk ABCD2 scores (0–3). CI indicates confidence interval; DWI, diffusion-weighted image; and TIA, transient ischemic attack.

Table 4. C-Statistics and Improvement of ABCD3 and ABCD3-I Scores in Comparison With ABCD2 Score

	7 Days		90 Days		3 Years	
	C-statistics (95% CI)	P Value	C-statistics (95% CI)	P Value	C-statistics (95% CI)	P Value
ABCD2	0.54 (0.46, 0.62)		0.57 (0.50, 0.63)		0.57 (0.51, 0.62)	
ABCD3	0.61 (0.54, 0.68)	0.02	0.60 (0.54, 0.66)	0.10	0.59 (0.53, 0.64)	0.26
ABCD3-I	0.66 (0.57, 0.74)	0.004	0.61 (0.54, 0.68)	0.26	0.61 (0.55, 0.66)	0.17
ABCD3-I(d, c/i)	0.67 (0.59, 0.75)	0.003	0.63 (0.56, 0.69)	0.12	0.61 (0.56, 0.67)	0.13
ABCD3-I(c/i)	0.67 (0.59, 0.74)	0.002	0.64 (0.58, 0.71)	0.02	0.62 (0.56, 0.67)	0.047

P values are calculated by the DeLong method, which compared each score with the ABCD2 score. (c) indicates carotid stenosis; CI, confidence interval; (d), diffusion-weighted image; and (i), intracranial arterial stenosis.

have suggested it is not useful for such prediction.^{13–15,25} One possible explanation for this discrepancy is that the usefulness of these scores may differ among study populations, ie, population-based study or hospital-based study, TIA diagnosed by nonexpert physicians or by stroke specialists, inpatients, or outpatients, and definite TIA or possible TIA.^{16,17} We found that the ABCD2 score was not useful to predict stroke after TIA in our cohort of patients with TIA. In this study, we included patients who were diagnosed as having definite TIA by stroke neurologists and underwent optimal treatment during hospitalization. In addition, carotid stenosis (18.6%) or both carotid stenosis and/or intracranial arterial stenosis (32.3%) were more prevalent in the subpopulation of the low-risk group than in the low-risk group in the previous study.⁷ These factors could have led to the failure of the score to predict future stroke.¹⁸

Dual TIA

This study revealed that a TIA event within 7 days before TIA (dual TIA) was a useful factor to predict short-term and long-term stroke, and that dual TIA significantly improved the performance of the ABCD2 score (Tables 4 and 5). The previous studies showed conflicting results concerning whether or not dual TIA can predict future stroke, with some studies suggesting

TIA had such a predictive ability^{7,13,25} and others suggesting it did not.^{26,27} The difference may have been related to a difference among the physicians making the diagnoses, that is, in some studies the diagnoses were made by stroke specialists,^{7,13,25} and in others they were made by general practitioners or emergency physicians at clinics and emergency departments.^{26,27} The accuracy of TIA determines the usefulness of dual TIA because the impact of dual TIA may be underestimated if patients with symptoms mimicking TIA are included as having TIA. Further validation studies will be needed to elucidate whether dual TIA is predictive of stroke after TIA.

Carotid Stenosis and Intracranial Arterial Stenosis

Recent studies have demonstrated that carotid stenosis^{14,28} or intracranial arterial stenosis^{8,9} were associated with recurrent stroke. The rate of procedures for carotid lesions was low in this study, which may have led to enhanced risk of this factor for future stroke. Carotid disease is less common, and carotid endarterectomy or carotid artery stenting is less frequently performed in Japan. In contrast, intracranial atherosclerotic stenosis is more prevalent in Asian population including the Japanese.^{29,30} Large artery intracranial atherosclerotic stenosis has emerged as the most common stroke subtype worldwide.^{29,30} Therefore, we constituted a novel score,

Table 5. Continuous NRI Reclassification From ABCD2 score

	7 Days		90 Days		3 Years	
	NRI (95% CI)	P Value	NRI (95% CI)	P Value	NRI (95% CI)	P Value
ABCD3, %	46.0 (17.9, 74.1)	0.001	28.2 (6.6, 50.0)	0.01	16.3 (–2.9, 35.5)	0.11
ABCD3-I, %	48.1 (19.1, 77.0)	0.001	12.9 (–11.1, 36.9)	0.30	14.9 (–4.9, 34.8)	0.15
ABCD3-I(d, c/i), %	52.3 (24.0, 80.5)	<0.001	36.8 (13.5, 60.2)	0.002	30.5 (11.5, 49.4)	0.002
ABCD3-I(c/i), %	59.9 (31.1, 88.7)	<0.001	39.5 (15.1, 63.9)	0.002	24.0 (3.9, 44.1)	0.02

Reclassification from the ABCD2 score. (c) indicates carotid stenosis; CI, confidence interval; (d), diffusion-weighted image; (i), intracranial arterial stenosis; and NRI, net reclassification improvement.

ABCD-I(d,c/i), by adding intracranial arterial stenosis to the ABCD3-I score and validated its usefulness. Carotid stenosis and/or intracranial arterial stenosis were significantly associated with stroke in not only the short term, but also in the long term for up to 3 years. Addition of intracranial arterial stenosis resulted in an improvement of the conventional scores to predict future stroke until 3 years after TIA (Table 5).

Abnormal DWI

It has been shown that abnormal DWI was a risk factor for short-term recurrence of stroke after TIA.^{31,32} In contrast, the present analysis did not show statistical significance of abnormal DWI as a risk factor for recurrent stroke. In this study, the rates of stroke occurrence after TIA in patients with normal and abnormal DWI were 5.9% and 8.8% within 7 days, and 10.2% and 11.3% within 90 days, respectively. The incidence in the abnormal DWI group was similar to that reported in the previous studies; however, that in the normal DWI group was 5 to 7 times higher than that in the previous study.³² This is probably because we included only patients with definite TIA in this study, leading to a high risk of stroke even in patients with normal DWI. If we enroll patients with probable TIA or possible TIA, TIA mimics would be included, leading to a lowered risk of stroke in the normal DWI group relative to that in the abnormal group. However, the larger number of cases could produce the difference because the risk of stroke in the abnormal DWI group tended to be high in the short term.

Short- and Long-Term Recurrences

The ABCD2 score was originally shown to predict short-term recurrence after TIA. The score may be useful to predict long-term risk of stroke after TIA although its usefulness has not been established.^{33,34} Our study showed that there were statistically significant differences at 90 days and 3 years in the risk of stroke between the ABCD2 low-risk and high-risk groups. In contrast, there has been no study concerning the usefulness of the ABCD3 and ABCD3-I scores to predict future stroke after TIA. In this study, we demonstrated striking findings that the stroke incidence after TIA was statistically different until 3 years according to the ABCD3 and ABCD3-I scores. The ABCD3-I(d,c/i) and the ABCD3-I(c/i) scores maintained significantly improved predictive power up to 3 years after TIA (Table 5). Because the *C*-statistics for long-term recurrence tended to be higher when abnormal DWI was excluded from the model, abnormal DWI may not be useful to predict long-term recurrence. The predictive power of these scores decayed because the follow-up period was prolonged (Table 4). To predict long-term recurrence after TIA, further improvement of the risk score is needed.

Strengths and Limitations

This study had some important strengths. The diagnosis of patients was accurate, and the imaging evaluation was performed in all patients without contraindication. As a Japanese nationwide survey reported that MRI was used for the diagnosis of TIA in 93% of patients, TIA is often diagnosed based on MRI in Japan.³⁵ The frequency of the neuroimaging and follow-up rates was remarkably high. Finally, the results of

this study should be of particular relevance because a validation of these scores in Asian populations is currently lacking. On the contrary, there were also limitations in this study. Subjects were inpatients hospitalized in the FSR, which could have caused a selection bias. However, most of patients with definite TIA may have been included in this study because admission to the hospitals was advised for all patients who were suspected to have TIA to identify the onset mechanism and start urgent treatment according to the Japanese guidelines.³⁶ The information about the treatment after discharge was unavailable. However, the treatments after discharge were performed by each practitioner, which reflects medical practice in real-world setting. All stroke events after TIA were not confirmed by neuroimaging. Although we adopted observational points and risk categories similar to those in the previous study,⁷ the fitness of each risk group was poor because of the different HR among risk factors. Finally, we cannot generalize an addition of intracranial arterial stenosis to the ABCD3-I score across ethnic groups because intracranial arterial stenosis is less prevalent in whites compared with Asians, and MRA is not commonly used worldwide.

In conclusion, the ABCD3 or ABCD3-I score, which includes dual TIA or carotid stenosis and DWI abnormality, improved the performance of the ABCD2 score to predict stroke recurrence in a cohort of patients with definite TIA. The consideration of intracranial arterial stenosis may have intensified the predictive ability of the score for recurrent stroke until 3 years after TIA. In patients with definite TIA, stroke recurrence was probably high even in the absence of abnormal DWI.

Because the *C*-statistics of each score were not high, ranging between 0.6 and 0.7, an improvement of the scores is needed. Further studies will be needed to elucidate the validity of the scores in a subpopulation of patients with normal DWI, if the diagnosis of TIA changes from a time-based diagnosis to a tissue-based one in the future.

Appendix

Fukuoka Stroke Registry Investigators

The participating hospitals in the Fukuoka Stroke Registry were the following: Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka-Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Steel Memorial Yawata Hospital, Japan Labor Health and Welfare Organization Kyushu Rosai Hospital.

The steering committee included the following: Takao Ishitsuka, MD (Steel Memorial Yawata Hospital); Shigeru Fujimoto, MD (Steel Memorial Yawata Hospital); Setsuro Ibayashi, MD (Seiai Rehabilitation Hospital); Kenji Kusuda, MD (Seiai Rehabilitation Hospital); Shuji Arakawa, MD (Japan Labour Health and Welfare Organization Kyushu Rosai Hospital); Kinya Tamaki, MD (Shinyoshizuka Hospital); Seizo Sadoshima, MD (Shinyoshizuka Hospital); Katsumi Irie, MD (Hakujuji Hospital); Kenichiro Fujii, MD (Fukuoka Red Cross Hospital); Yasushi Okada, MD (National Hospital Organization Kyushu Medical Center); Masahiro Yasaka, MD (National Hospital Organization Kyushu Medical Center); Tetsuhiko Nagao, MD (Midorino

Clinic); Hiroaki Ooboshi, MD (Fukuoka Dental College Medical and Dental Hospital); Tsuyoshi Omae, MD (Imazu Red Cross Hospital); Kazunori Toyoda, MD (National Cardiovascular Center); Hiroshi Nakane, MD (National Hospital Organization Fukuoka-Higashi Medical Center); Hiroshi Sugimori, MD (Kyushu University Hospital); Kenji Fukuda, MD (Kurume University School of Medicine); Ryu Matsuo, MD (Kyushu University Hospital); Junya Kuroda, MD (Kyushu University Hospital); Yoshihisa Fukushima, MD (St. Mary's Hospital).

Acknowledgments

We thank all the FSR investigators and their hospitals for their participation in this study. We are grateful to Associate Professor Hitoshi Inoue (Research Institute for Information Technology, Kyushu University) for the technical support for securing FSR Data Collection System and all the clinical research coordinators (Hisayama Research Institute for Lifestyle Diseases) for their help in obtaining informed consent and collecting clinical data.

Sources of Funding

This study was supported by a Grant-in-Aid for Scientific Research (A 22249069) and Coordination, Support and Training Program for Translational Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Disclosures

None.

References

- Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901–2906.
- Lisabeth LD, Ireland JK, Risser JM, Brown DL, Smith MA, Garcia NM, et al. Stroke risk after transient ischemic attack in a population-based setting. *Stroke*. 2004;35:1842–1846.
- Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Early use of Existing Preventive Strategies for Stroke (EXPRESS) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370:1432–1442.
- Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. *Lancet Neurol*. 2009;8:235–243.
- Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366:29–36.
- Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369:283–292.
- Merwick A, Albers GW, Amarenco P, Arsava EM, Ay H, Calvet D, et al. Addition of brain and carotid imaging to the ABCD² score to identify patients at early risk of stroke after transient ischaemic attack: a multi-centre observational study. *Lancet Neurol*. 2010;9:1060–1069.
- Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD; Calgary Stroke Program. CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke: results of the prospective CATCH study. *Stroke*. 2012;43:1013–1017.
- Poisson SN, Nguyen-Huynh MN, Johnston SC, Furie KL, Lev MH, Smith WS. Intracranial large vessel occlusion as a predictor of decline in functional status after transient ischemic attack. *Stroke*. 2011;42:44–47.
- Fothergill A, Christianson TJ, Brown RD Jr, Rabinstein AA. Validation and refinement of the ABCD² score: a population-based analysis. *Stroke*. 2009;40:2669–2673.
- Cancelli I, Janes F, Gigli GL, Perelli A, Zanchettin B, Canal G, et al. Incidence of transient ischemic attack and early stroke risk: validation of the ABCD² score in an Italian population-based study. *Stroke*. 2011;42:2751–2757.
- Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40:2276–2293.
- Purroy F, Jiménez Caballero PE, Gorospe A, Torres MJ, Alvarez-Sabin J, Santamarina E, et al; Stroke Project of the Spanish Cerebrovascular Diseases Study Group. Prediction of early stroke recurrence in transient ischemic attack patients from the PROMAPA study: a comparison of prognostic risk scores. *Cerebrovasc Dis*. 2012;33:182–189.
- Sheehan OC, Kyne L, Kelly LA, Hannon N, Marnane M, Merwick A, et al. Population-based study of ABCD² score, carotid stenosis, and atrial fibrillation for early stroke prediction after transient ischemic attack: the North Dublin TIA study. *Stroke*. 2010;41:844–850.
- Perry JJ, Sharma M, Sivilotti ML, Sutherland J, Symington C, Worster A, et al. Prospective validation of the ABCD² score for patients in the emergency department with transient ischemic attack. *CMAJ*. 2011;183:1137–1145.
- Giles MF, Rothwell PM. Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD² transient ischemic attack risk scores. *Stroke*. 2010;41:667–673.
- Sheehan OC, Merwick A, Kelly LA, Hannon N, Marnane M, Kyne L, et al. Diagnostic usefulness of the ABCD² score to distinguish transient ischemic attack and minor ischemic stroke from noncerebrovascular events: the North Dublin TIA Study. *Stroke*. 2009;40:3449–3454.
- Amarenco P, Labreuche J, Lavallée PC. Patients with transient ischemic attack with ABCD² <4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD² ≥4. *Stroke*. 2012;43:863–865.
- Kamouchi M, Matsuki T, Hata J, Kuwashiro T, Ago T, Sambongi Y, et al; FSR Investigators. Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: the Fukuoka Stroke Registry. *Stroke*. 2011;42:2788–2794.
- Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J, Nakane H, et al; FSR Investigators. Proteinuria and clinical outcomes after ischemic stroke. *Neurology*. 2012;78:1909–1915.
- Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetol Int*. 2010;1:2–20.
- Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
- Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11–21.
- Nakajima M, Hirano T, Naritomi H, Minematsu K. Symptom progression or fluctuation in transient ischemic attack patients predicts subsequent stroke. *Cerebrovasc Dis*. 2010;29:221–227.
- Johnston SC, Sidney S, Bernstein AL, Gress DR. A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. *Neurology*. 2003;60:280–285.
- Paul NL, Simoni M, Chandratheva A, Rothwell PM. Population-based study of capsular warning syndrome and prognosis after early recurrent TIA. *Neurology*. 2012;79:1356–1362.
- Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabín J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. *Stroke*. 2007;38:3225–3229.
- Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke*. 2008;39:2396–2399.
- Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol*. 2013;12:1106–1114.

31. Giles MF, Albers GW, Amarenco P, Arsava MM, Asimos A, Ay H, et al. Addition of brain infarction to the ABCD2 Score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. *Stroke*. 2010;41:1907–1913.
32. Giles MF, Albers GW, Amarenco P, Arsava EM, Asimos AW, Ay H, et al. Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. *Neurology*. 2011;77:1222–1228.
33. Wijnhoud AD, Maasland L, Lingsma HF, Steyerberg EW, Koudstaal PJ, Dippel DW. Prediction of major vascular events in patients with transient ischemic attack or ischemic stroke: a comparison of 7 models. *Stroke*. 2010;41:2178–2185.
34. Yang J, Fu JH, Chen XY, Chen YK, Leung TW, Mok V, et al. Validation of the ABCD2 score to identify the patients with high risk of late stroke after a transient ischemic attack or minor ischemic stroke. *Stroke*. 2010;41:1298–1300.
35. Uehara T, Minematsu K. Clinical practice of transient ischemic attack in Japan: a questionnaire survey to stroke teaching hospitals certified by Japan Stroke Society. *Jpn J Stroke*. 2010;32:710–718.
36. Shinohara Y, Yanagihara T, Abe K, Yoshimine T, Fujinaka T, Chuma T, et al. II. Cerebral infarction/transient ischemic attack (TIA). *J Stroke Cerebrovasc Dis*. 2011;20:31–73.

ABCD3 and ABCD3-I Scores Are Superior to ABCD2 Score in the Prediction of Short- and Long-Term Risks of Stroke After Transient Ischemic Attack
Takuya Kiyohara, Masahiro Kamouchi, Yasuhiro Kumai, Toshiharu Ninomiya, Jun Hata, Sohei Yoshimura, Tetsuro Ago, Yasushi Okada and Takanari Kitazono
for the FSR investigators

Stroke. 2014;45:418-425; originally published online December 12, 2013;
doi: 10.1161/STROKEAHA.113.003077
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/45/2/418>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>