Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2012;33:182–189
DOI: 10.1159/000334771

Received: June 28, 2011
Accepted: October 21, 2011
Published online: January 7, 2012

Prediction of Early Stroke Recurrence in Transient Ischemic Attack Patients from the PROMAPA Study: A Comparison of Prognostic Risk Scores

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Key Words
Transient ischemic attack · Prognosis · Outcome · Stroke recurrence

Abstract
Background: Several clinical scales have been developed for predicting stroke recurrence. These clinical scores could be extremely useful to guide triage decisions. Our goal was to compare the very early predictive accuracy of the most relevant clinical scores [age, blood pressure, clinical features and duration of symptoms (ABCD) score, ABCD and diabetes (ABCD2) score, ABCD and brain infarction on imaging score, ABCD2 and brain infarction on imaging score, ABCD and prior TIA within 1 week of the index event (ABCD3) score, California Risk Score, Essen Stroke Risk Score and Stroke Prognosis Instrument II] in consecutive transient ischemic attack (TIA) patients. ***Methods:*** Between April 2008 and December 2009, we included 1,255 consecutive TIA patients from 30 Spanish stroke centers (PROMAPA study). A neurologist treated all patients within the first 48 h after symptom onset. The duration and typology of clinical symptoms, vascular risk factors and etiological work-ups were prospectively recorded in a case report form in order to calculate established

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prognostic scores. We determined the early short-term risk of stroke (at 7 and 90 days). To evaluate the performance of each model, we calculated the area under the receiver operating characteristic curve. Cox proportional hazards multivariate analyses determining independent predictors of stroke recurrence using the different components of all clinical scores were calculated. ***Results:*** We calculated clinical scales for 1,137 patients (90.6%). Seven-day and 90-day stroke risks were 2.6 and 3.8%, respectively. Large-artery atherosclerosis (LAA) was observed in 190 patients (16.7%). We could confirm the predictive value of the ABCD3 score for stroke recurrence at the 7-day follow-up [0.66, 95% confidence interval (CI) 0.54–0.77] and 90-day follow-up (0.61, 95% CI 0.52–0.70), which improved when we added vascular imaging information and derived ABCD3V scores by assigning 2 points for at least 50% symptomatic stenosis on carotid or intracranial imaging (0.69, 95% CI 0.57–0.81, and 0.63, 95% CI 0.51–0.69, respectively). When we evaluated each component of all clinical scores using Cox regression analyses, we observed that prior TIA and LAA were independent predictors of stroke recurrence at the 7-day follow-up [hazard ratio (HR) 3.97, 95% CI 1.91–8.26, $p < 0.001$, and HR 3.11, 95% CI 1.47–6.58, $p = 0.003$, respectively] and 90-day follow-up (HR 2.35, 95% CI 1.28–4.31, $p = 0.006$, and HR 2.20, 95% CI 1.15–4.21, $p = 0.018$, respectively). ***Conclusion:*** All published scores that do not take into account vascular imaging or prior TIA when identifying stroke risk after TIA failed to predict risk when applied by neurologists. Clinical scores were not able to replace extensive emergent diagnostic evaluations such as vascular imaging, and they should take into account unstable patients with recent prior transient episodes.

Introduction

Transient ischemic attack (TIA) is a widespread disease with an estimated annual incidence as high as 64 per 100,000 [1]. For this reason, many different kinds of physicians treat these patients, from primary care or emergency department professionals to stroke unit neurologists. Moreover, TIA is associated with a high risk of early recurrent stroke [2], with stroke rates of more than 20% in subgroups of patients with large-artery atherosclerosis (LAA) [3–6]. Some clinical prediction scores, such as the age, blood pressure, clinical features and duration of symptoms (ABCD) score [7], the ABCD and diabetes (ABCD2) score [8], the ABCD2 and brain infarction on imaging (ABCD2I) score [9], the California Risk Score [10], the Essen Stroke Risk Score (ESRS) [11–13] and the Stroke Prognosis Instrument II (SPI-II) [14], have been developed to improve stratification of recurrent stroke risk. These clinical scores could be extremely useful for primary care and emergency department physicians to guide triage decisions. ABCD and ABCD2 scales have been the subject of multiple external validation studies with inconsistent results, ranging from limited to excellent predictive ability, due to extremely varied testing methodologies [5, 15–25]. There is limited information about the external validity of the other predictive scores, but they do have some common characteristics. They are simple and easy to apply, but they do not take into account vascular mechanisms and do not incorporate vascular imaging data. Recently, new prognostic scores have been proposed. The ABCD3 incorporates the variable of prior TIA within 1 week of the index event into the ABCD system, whereas the ABCD3I also incorporates information from vascular carotid imaging and brain imaging (abnormal diffusion-weighted imaging) findings [26].

Using a prospective multicenter registry of more than 1,000 TIA patients, we investigated the capacity of the existing prognostic scores and the new ABCD3 scale to accurately predict stroke recurrence in a cohort of patients evaluated by a neurologist.

Methods

We included patients from 30 Spanish stroke units between January 2008 and December 2009. A TIA was defined as a reversible episode of neurological deficit of ischemic origin that resolved completely within 24 h [27]. A neurologist treated all patients within the first 48 h after symptom onset. We excluded patients with a modified Rankin Scale score >3 and/or patients with a diagnosis other than TIA. The modified Rankin Scale score was measured at baseline, always after symptom resolution. Patients with previous stroke or TIA were also included. Patients who first sought medical attention or had brain imaging for a stroke recurrence rather than the index TIA were excluded.

The study was approved by the ethics committee of the Arnau de Vilanova University Hospital and all involved institutions. Written informed consent was obtained from all study participants. The duration and typology of clinical symptoms, vascular risk factors and etiological work-ups were prospectively recorded in a case report form in order to calculate the following established prognostic scores: ABCD, ABCD2, ABCD2I, ABCD and brain infarction on imaging, ABCD3, ESRS, SPI-II and the California scale (table 1). Prior TIA was defined as the occurrence of at least 2 TIAs – the index TIA and one other TIA – in the 7 days prior to the index event [26]. We also considered adding vascular information to the ABCD3 score. Therefore, we defined the ABCD3V score by assigning 2 points for LAA. LAA was defined as >50% narrowing of the ipsilateral internal carotid artery lumen or intracranial vessel lumen on imaging, including Doppler or duplex ultrasound, magnetic resonance angiogram (MRA) or com-

Table 1. Point score of clinical scales for recurrent stroke

Variable	California Risk Score	ABCD	ABCD2	ABCDI	ABCD2I	ABCD3	ABCD3V	SPI-II	ESRS
Age									
≥60 years		1	1	1	1	1	1		
>60 years	2								
>70 years								2	
65–75 years									1
>75 years									2
Diabetes mellitus	1	–	1	–	1	1	1	3	1
Hypertension	–	1	1	1	1	1	1	1	1
Coronary heart disease	–	–	–	–	–	–	–	1	1
Cardiac failure	–	–	–	–	–	–	–	3	–
Previous stroke	–	–	–	–	–	–	–	3	–
Symptom duration									
>10 min	1								
0–10 min		0	0	0	0	0	0	–	–
10–60 min		1	1	1	1	1	1		
≥60 min		2	2	2	2	2	2		
Motor weakness	1	2	2	2	2	2	2	–	–
Speech disturbance	1	1	1	1	1	1	1	–	–
Chronic ischemic lesion on CT scan	–	–	–	1	1	1	1	–	–
Smoking	1	–	–	–	–	–	–	–	1
Prior TIA	–	–	–	–	–	2	2	–	1
Peripheral arterial disease	–	–	–	–	–	–	–	–	1
LAA	–	–	–	–	–	–	2	–	–

puterized tomographic angiography (CTA). Extracranial studies were performed in all cases (ultrasound 95%, MRA 15%, CTA 4.5%). Intracranial studies were performed in 786 cases (69.1%; ultrasound 69.1%, MRA 14.3%, CTA 3.9%). Neuroimaging was performed in all cases. MRI evaluation was not a study requirement, and patient selection for MRI was not systematic but based on the practice of the individual clinician and resource availability. ACBCDI and ABCD2I were calculated by assigning 1 point for the presence of any infarction on CT imaging (given the unreliability of distinction between acute and old infarction) irrespective of whether it was appropriate to the infarction causing the presenting symptoms. Chronic small vessel ischemic changes, like leukoaraiosis, were not scored.

Hypertension was defined as a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or current use of antihypertensive medications. Cigarette smoking was defined as present if the patient reported smoking cigarettes during the past 5 years. Hypercholesterolemia was defined as a total cholesterol concentration >220 mg/dl or the current use of lipid-lowering agents. Diabetes mellitus was defined as a history of fasting glucose >126 mg/dl or the current use of hypoglycemic medication. History of diagnosed coronary artery disease, peripheral arterial disease, atrial fibrillation and valvular heart disease was also recorded.

All baseline data were centrally monitored, and queries were sent to the enrolling physicians.

The 30 centers consecutively documented 1,255 TIA patients. We excluded 104 patients with missing data or without information on the underlying TIA mechanism or vascular pathology.

The primary outcome measure was the occurrence of a subsequent stroke at the 7-day and 90-day follow-up. Secondary endpoints consisted of the detection of LAA and a composite endpoint (CE) consisting of stroke recurrence within 7 days. Recurrence of TIA was not considered an endpoint. Clinical assessments were performed at 7 and 90 days by a neurovascular neurologist from each participating center.

Statistical analysis was performed with the SPSS statistical package, version 15.0. The statistical significance of intergroup differences was assessed using the χ^2 test for categorical variables and Student's t test and the Mann-Whitney U test for continuous variables. Receiver operating characteristic curves were obtained for each model, plotting specificity against sensitivity. Discriminatory power was calculated from the area under the receiver operating characteristic curve (AUC) for a 95% confidence interval (CI) using standard methods. Ideal discrimination produces an AUC of 1.0, whereas discrimination that is no better than chance produces an AUC of 0.5. Cox proportional-hazards multivariate analyses determining independent predictors of the 7-day and 90-day risk of stroke recurrence using the different components of all clinical scores were performed. Moreover, binomial regression multivariate analyses were used to identify predictors for LAA. A probability value <0.05 was considered significant.

Results

A total of 1,137 patients were included in the study. The characteristics of the enrolled patients are shown in table 2. Mean age was 68.6 (SD 13.1) years. A total of 674 subjects (59.3%) were male, and hypertension, the principal risk factor, was present in 716 (63.0%). Mean, SD and median values for prognostic clinical scores are also shown in table 2. LAA was found in 190 patients (16.7%); extracranial stenosis >50% was seen in 145 patients (12.8%) and intracranial stenosis in 64 of the 786 patients with intracranial studies (8.1%). Ninety-day follow-up was achieved in 1,105 cases (97.2%). Overall, 29 patients (2.6%) had had a recurrent stroke by follow-up at day 7. New recurrent strokes within the first 90 days after the index TIA event were recorded in 43 patients (3.9%). Therefore, the CE was observed in 208 patients (18.3%).

The AUC values for the prediction of stroke recurrence, LAA and the CE are shown in table 3. ABCD3 and especially ABCD3V scores were able to identify a risk of stroke recurrence at the 7-day and 90-day follow-up with better than random (>0.5) discrimination. If the presence of LAA or the CE was considered, the ESRS was marginally superior.

When we evaluated each component of all clinical scores using Cox regression analyses (table 4), we observed that prior TIA and LAA were independent predictors of stroke recurrence at the 7-day follow-up [hazard ratio (HR) 3.97, 95% CI 1.91–8.26, $p < 0.001$, and HR 3.11, 95% CI 1.47–6.58, $p = 0.003$, respectively] and 90-day follow-up (HR 2.35, 95% CI 1.28–4.31, $p = 0.006$, and HR 2.20, 95% CI 1.15–4.21, $p = 0.018$, respectively). Motor weakness was also an independent predictor of stroke recurrence at the 90-day follow-up (HR 1.45, 95% CI 1.03–2.04, $p = 0.035$). LAA was associated with prior TIA [odds ratio (OR) 2.01, 95% CI 1.44–2.80, $p < 0.001$] and motor weakness (OR 1.20, 95% CI 1.02–1.41, $p = 0.029$). Previous stroke (OR 1.26, 95% CI 1.11–1.44, $p < 0.001$) and previous peripheral arterial disease (OR 3.11, 95% CI 1.74–5.56, $p < 0.001$) were also independent predictors of the presence of LAA.

Table 2. Characteristics of the patients

Variable	
Risk factors, n	
Male	674 (59.3)
Hypertension	716 (63.0)
Previous stroke	235 (19.0)
Diabetes mellitus	291 (25.6)
Coronary disease	181 (15.9)
Hypercholesterolemia	430 (37.9)
Atrial fibrillation	128 (11.3)
Smoking (current or past 5 years)	285 (25.1)
Cardiac failure	52 (4.6)
Peripheral arterial disease	62 (5.5)
Alcoholism	85 (7.5)
Clinical features, n	
Prior TIA	274 (24.1)
Speech impairment	734 (64.6)
Motor weakness	667 (58.7)
Isolated sensory symptoms	88 (7.7)
Vertebrobasilar symptoms	136 (12.0)
Etiological subtypes, n	
LAA	190 (16.7)
Cardioembolism	242 (21.3)
Small-vessel disease	299 (26.3)
Undetermined cause	391 (34.4)
Unhabitual	15 (1.3)
Prognostic clinical scales, mean score	
ABCD	4.39 (1.18, 5.00)
ABCD2	4.65 (1.32, 5.0)
ABCDI	4.70 (1.32, 5.00)
ABCD2I	4.96 (1.46, 5.00)
ABCD3	5.13 (1.50, 5,00)
ABCD3V	5.46 (1.77, 5,00)
ESRS	2.64 (1.41, 3.00)
SPI-II	3.34 (2.66, 3.00)
California Risk Score	3.12 (1.05, 3.00)
Discharge treatment, n	
Aspirin	663 (58.3)
Clopidogrel	320 (28.1)
Triflusal	17 (1.5)
Anticoagulation	220 (19.3)
Statins	715 (62.9)
Renin-angiotensin system blockers	556 (48.9)
Carotid endarterectomy or carotid angioplasty	66 (5.8)

Values in parentheses represent percentages or SD and median, as appropriate.

Discussion

This was a prospective multicenter study that directly compared the usefulness of the most widely used predictive clinical scores in a large cohort of patients with TIA. Clinical scores are primarily used to determine the risk of recurrent strokes and to help physicians in their daily clinical routine because patients with TIA are a heterogeneous group in terms of prognosis. We established a short follow-up endpoint because it is well known that the risk of stroke recurrence is highest within the first 7

Table 3. Predictive accuracy of clinical scores for recurrent stroke at the 7- and 90-day follow-up, LAA and the CE

Clinical score	Stroke recurrence at 7-day follow-up		Stroke recurrence at 90-day follow-up		LAA		CE at 7 days	
	AUC	p	AUC	p	AUC	p	AUC	p
California Risk Score	0.52 (0.42–0.63)	0.656	0.54 (0.45–0.63)	0.374	0.58 (0.53–0.62)	0.001	0.57 (0.53–0.61)	0.001
ABCD	0.57 (0.46–0.68)	0.213	0.55 (0.46–0.64)	0.245	0.57 (0.52–0.61)	0.005	0.56 (0.52–0.60)	0.008
ABCD2	0.56 (0.45–0.66)	0.300	0.55 (0.46–0.64)	0.243	0.58 (0.54–0.63)	<0.001	0.57 (0.53–0.62)	0.001
ABCDI	0.56 (0.44–0.67)	0.311	0.56 (0.45–0.67)	0.285	0.59 (0.55–0.64)	<0.001	0.58 (0.54–0.63)	<0.001
ABCD2I	0.56 (0.45–0.67)	0.285	0.55 (0.44–0.65)	0.415	0.61 (0.56–0.65)	<0.001	0.60 (0.55–0.63)	<0.001
ABCD3	0.66 (0.57–0.81)	0.004	0.61 (0.52–0.70)	0.015	0.62 (0.57–0.66)	<0.001	0.62 (0.57–0.66)	<0.001
ABCD3V	0.69 (0.57–0.81)	<0.001	0.63 (0.54–0.73)	0.003	–	–	–	–
SPI-II	0.50 (0.41–0.59)	0.986	0.51 (0.43–0.60)	0.774	0.61 (0.57–0.65)	<0.001	0.60 (0.56–0.64)	<0.001
ESRS	0.60 (0.51–0.70)	0.056	0.58 (0.49–0.66)	0.086	0.63 (0.59–0.67)	<0.001	0.63 (0.59–0.67)	<0.001

Values in parentheses represent 95% CIs.

Table 4. Multivariate analyses determining independent predictors of the 7- and 90-day risk of stroke recurrence and LAA using the different components of all clinical scores

Variable	Stroke recurrence at 7-day follow-up			Stroke recurrence at 90-day follow-up			LAA		
	HR	95% CI	p	HR	95% CI	p	OR	95% CI	p
Age	1.01	0.98–1.05	0.392	1.00	0.97–1.03	0.987	1.01	0.99–1.03	0.160
Diabetes mellitus	0.78	0.31–1.98	0.600	0.91	0.44–1.85	0.785	1.17	0.80–1.70	0.422
Hypertension	1.75	0.51–6.06	0.375	1.95	0.67–5.65	0.220	1.36	0.81–2.28	0.251
Coronary heart disease	0.65	0.19–2.23	0.489	1.28	0.57–2.85	0.557	1.19	0.77–1.85	0.425
Cardiac failure	0.69	0.91–5.17	0.715	1.41	0.43–4.67	0.571	1.00	0.47–2.13	0.99
Previous stroke	0.92	0.64–1.32	0.638	0.92	0.70–1.22	0.566	1.26	1.11–1.44	<0.001
Prior TIA	3.97	1.91–8.26	<0.001	2.35	1.28–4.31	0.006	2.01	1.44–2.80	<0.001
Symptom duration	1.14	0.66–1.96	0.637	0.93	0.61–1.43	0.752	1.04	0.82–1.33	0.733
Motor weakness	1.50	0.98–2.30	0.062	1.45	1.03–2.04	0.035	1.20	1.02–1.41	0.029
Speech disturbance	0.66	0.31–1.37	0.265	1.07	0.57–1.99	0.830	0.95	0.68–1.33	0.745
Infarction on CT scan	1.14	0.51–2.55	0.748	1.19	0.62–2.30	0.603	1.22	0.85–1.75	0.278
Smoking	1.05	0.40–2.74	0.925	0.84	0.37–1.89	0.671	1.45	0.95–2.20	0.082
Peripheral arterial disease	0.53	0.07–4.10	0.545	0.30	0.04–2.28	0.567	3.11	1.74–5.56	<0.001
LAA	3.11	1.47–6.58	0.003	2.20	1.15–4.21	0.018	–	–	–

days after the index TIA in population-based studies without urgent treatment [2]. In our prospective study, no clinical scores which do not take into account vascular imaging or prior TIA were able to stratify the risk of recurrent stroke at the 7-day or 90-day follow-up. Only the ABCD3 score and especially the ABCD3V score, derived from ABCD3 by adding 2 points for LAA, were able to select patients with a high risk of early stroke recurrence from a cohort of patients evaluated and treated by stroke neurologists. However, our cohort had some differences from the original derivation studies. The ABCD and ABCD2 scales [7, 8, 28] were published using data from population-based TIA registries, while the California Risk Score [10] used data from a cohort study of patients diagnosed with TIA in the emergency department. Patients were identified when a TIA diagnosis was entered into the emergency department database, with further data retrospectively obtained from medical records. Although a recent meta-analysis of the ABCD system has reported a satisfactory predictive ability for 7-day

risk of stroke recurrence [16], differences could be explained by the clinical specialty of the physician who performed the initial evaluation. Direct clinical assessment by a stroke neurologist could have reduced misdiagnosis. Sheehan et al. [25] noted an adequate predictive utility of the ABCD2 score in patients with a suspected TIA diagnosed by a non-specialist but not in TIA cases confirmed by stroke specialists. Therefore, it is likely that the predictive power of the clinical scores is based on their diagnostic discrimination. Moreover, the original ABCD3I score takes into account only carotid stenosis >50% and diffusion-weighted imaging abnormalities. In our study, we also considered symptomatic intracranial stenosis because there is enough evidence that intracranial vascular imaging data provide important prognostic information [29]. Unfortunately, diffusion-weighted imaging was not an inclusion criterion for our study and therefore we could not add these data for all patients.

The California Risk Score [10] and the different subtypes of the ABCD score [7, 8, 28] have been validated for short-term prognosis, whereas the SPI-II and ESRS were designed for longer follow-up periods. In the early phase after TIA stroke, the recurrence risk is highest in patients with unstable vascular etiology [3], while in the later phase, stroke risk may be determined by established vascular risk factors or other etiologies [30]. Previously, Weimar et al. [12] described a good relationship between the SPI-II and ESRS scores and the risk of stroke recurrence within the first year after TIA and nondisabling stroke.

Individualized clinical judgment and optimal management of a TIA should include information about the underlying mechanism of the TIA. LAA is the main independent predictor of poor prognosis in these patients [3–5], but we did not find a good correlation between clinical scales and the presence of this etiology or a combined endpoint.

The California and ABCD scales take into account more clinical characteristics of events than vascular risk factors. On the other hand, the SPI-II and ESRS mainly incorporate traditional vascular risk factors. Information on both clinical characteristics and traditional vascular risk factors seems to be important. LAA is associated with vascular risk factors [3], whereas clinical symptoms could accurately discriminate true brain ischemia events from noncerebrovascular events [25, 31].

When we evaluated each component of all the clinical scores, prior TIA and LAA were the main independent predictors of stroke recurrence at the 7- and 90-day follow-up. Recent prior TIA was associated with a high risk of early stroke because of repeated emboli from this unstable situation. Therefore, triage decisions based on clinical variables should take these two variables into account.

We believe our findings are valid, but our study does have some shortcomings. We included patients from 30 stroke centers in Spain. Although the initial proposal adhered to international guidelines [32–35], there may have been variations in patient study and management methods. In addition, we observed a low rate of stroke recurrence. The early evaluation of TIA patients by stroke neurologists (within the first 48 h of symptom onset) and the immediate initiation of preventive treatment may have greatly reduced the risk of subsequent strokes. Nevertheless, a larger cohort would have improved the generalizability of our findings. Moreover, recent evidence suggests that early stroke risk after a TIA may also be estimated from prediction scores based on diffusion MRI, such as the ABCD3I [9, 26, 36–38], but we could not evaluate this feature in all patients. Furthermore, intracranial lesions were not studied in all cases. Cases without intracranial studies were included in the statistical analyses. Therefore, we assume that some patients classified as having TIA of undetermined cause could have had symptomatic intracranial stenosis.

Our results show that existing predictive scores that use only clinical characteristics failed to identify patients with a high risk of stroke recurrence and high-risk stroke mechanisms. They were not able to replace extensive emergent diagnostic evaluations, such as vascular imaging, and they should take into account unstable patients with recent prior episodes.

Disclosure Statement

This study was sponsored by Sanofi-Aventis. Dr. F. Purroy receives grants from the Instituto de Salud Carlos III-programa de Intensificación and FIS Number PIO81398. Dr. B. Fuentes receives grants from the Instituto de Salud Carlos III-programa de Intensificación and the Agencia Laín Entralgo-Comunidad de Madrid (I3SNS). Dr. J. Masjuán and Dr. J.A. Egido serve on the scientific advisory board for Boehringer Ingelheim. The remaining authors have no disclosures to report.

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