Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack

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Summary

Background We aimed to validate two similar existing prognostic scores for early risk of stroke after transient ischaemic attack (TIA) and to derive and validate a unified score optimised for prediction of 2-day stroke risk to inform emergency management.

Methods The California and ABCD scores were validated in four independent groups of patients (n=2893) diagnosed with TIA in emergency departments and clinics in defined populations in the USA and UK. Prognostic value was quantified with c statistics. The two groups used to derive the original scores (n=1916) were used to derive a new unified score based on logistic regression.

Findings The two existing scores predicted the risk of stroke similarly in each of the four validation cohorts, for stroke risks at 2 days, 7 days, and 90 days (c statistics 0·60–0·81). In both derivation groups, c statistics were improved for a unified score based on five factors (age ≥60 years [1 point]; blood pressure ≥140/90 mm Hg [1]; clinical features: unilateral weakness [2], speech impairment without weakness [1]; duration ≥60 min [2] or 10–59 min [1]; and diabetes [1]). This score, ABCD^2, validated well (c statistics 0·62–0·83); overall, 1012 (21%) of patients were classified as high risk (score 6–7, 8·1% 2-day risk), 2169 (45%) as moderate risk (score 4–5, 4·1%), and 1628 (34%) as low risk (score 0–3, 1·0%).

Implications Existing prognostic scores for stroke risk after TIA validate well on multiple independent cohorts, but the unified ABCD^2 score is likely to be most predictive. Patients at high risk need immediate evaluation to optimise stroke prevention.

Lancet 2007; 369: 283–92

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Introduction

About 240 000 transient ischaemic attacks (TIAs) are diagnosed every year in the USA,[1] and about 70 000 in the UK,[2] with an overall incidence approaching that of ischaemic stroke. Patients with TIA are generally unstable, with recent studies showing that 4–20% will have a stroke within 90 days after a TIA, half within the first 2 days.[1,3–8] However, most patients with TIA will have a benign short-term course. Identification of those at highest and lowest risk of stroke in the first days and weeks after a TIA would allow appropriate use of costly secondary prevention strategies, including hospital admission.[9–11] Guideline recommendations for admission after TIA are vague[11,12] and practice is highly variable,[13] with some institutions admitting most patients and others none.

Two prognostic scores for short-term risk of stroke after TIA have been proposed: the California score[3] and the ABCD score.[14] Both scores rely on summation of points associated with clinical factors independently predictive of stroke risk, and have several factors in common. However, validation of the California score has only been published in abstract form, and although the ABCD score validated well in two quite small independent Oxfordshire cohorts,[14] and in a Greek cohort,[15] more validations by independent investigators are needed. Prognostic scores often validate less well than in the original studies when applied to different populations assembled by independent investigators.[16] Furthermore, the California score was developed to predict stroke within 90 days and the ABCD score predicts 7-day risk of stroke, whereas the 2-day risk is often most relevant for decisions about necessity of urgent evaluation and observation; complete diagnostic evaluation and treatment would be difficult to implement within 48 h of a TIA in the outpatient setting.

We therefore aimed to validate the two existing prognostic scores in large independently assembled groups from different populations, comparing predictions of stroke risk at 2, 7, and 90 days. To assess the probable generalisability of the validations, we used groups recruited from emergency departments, specialist clinics, and primary care. Furthermore, by combining results from the original groups used to derive the California and ABCD prognostic scores, we sought to generate a new unified score that would improve prediction of risk of stroke in the 2 days after TIA, and thus create a sole standard for use in clinical care. We then validated the new score in four independent cohorts from California and Oxford, UK, and compared its effectiveness with that of the original scores.

Methods

Study groups

All study protocols were approved by the appropriate local review boards. To develop and validate generalisable prognostic scores, the study populations included various clinical settings in two dissimilar populations, from the Kaiser-Permanente Medical Care Plan

(KPMCP) in Northern California, USA, and from Oxfordshire, UK, studied over a range of periods (table 1). Characteristics of the derivation cohorts from Northern California and Oxford have been detailed elsewhere.[3,4,14] Each study evaluated risk of stroke after an initial TIA in a clearly defined group that was representative of the local population and used rigorous methods to assure complete ascertainment of events during follow-up. In the California group, potential predictors of stroke were identified from review of the records of the initial treating doctor. For the California study, all inpatient and outpatient records were reviewed for follow-up events, for hospitals inside and outside KPMCP. In the Oxford cohort, all patients were assessed shortly after the TIA by a study neurologist and were followed-up by face-to-face interview with a study research nurse or neurologist at 1 month and again at 6, 12, and 24 months. All patients with suspected strokes during follow-up were re-assessed and investigated by a study neurologist.

Prognostic scores were tested in four separate validation groups (table 1). In KPMCP, we identified two random samples of patients diagnosed with TIA in 16 hospitals, either in emergency departments or in outpatient clinics. Those diagnosed in clinics had appointments scheduled within 1 week of TIA symptoms. Otherwise, methods of ascertainment, documentation, and follow-up were identical to those used in the derivation group.[3] The Oxford validation sets were a population-based group derived from patients of 63 family doctors[5] and a group of all patients diagnosed with possible TIA seen in a hospital-based TIA referral clinic, as previously described.[14] In both Oxford validation groups, all patients were assessed shortly after the TIA by a study neurologist and all were followed-up by face-to-face interview with a study research nurse or neurologist at 1 month and again at 6, 12, and 24 months. All patients with suspected strokes during follow-up were re-assessed and investigated by a study neurologist. Additionally, since all strokes in the population-based Oxford group were simultaneously being ascertained as part of a stroke incidence study, any follow-up events that might have been missed on follow-up were identified in this way.

In all groups, for the purpose of the present study the diagnosis of TIA was based entirely on the opinion of the initial treating doctor (table 1) so that results would be generalisable to patients not diagnosed by a stroke specialist. To reflect the way the score would be used in practice, timing of events during follow-up was measured from the time of presentation with TIA rather than from onset of symptoms. Stroke was defined as a rapidly developed clinical symptom of focal (or occasionally global) disturbance of cerebral function, lasting more than 24 h or until death, with no apparent non-vascular cause,[17] that was clearly distinguishable from the event leading to the initial diagnosis of TIA. The diagnosis of stroke was confirmed by a study neurologist, on the basis of either review of medical and electronic records (including imaging reports and all inpatient and outpatient records) in California or by actual face-to-face evaluation and review of records in Oxford.

Validation of previous prognostic scores

California and ABCD scores were originally generated by simplifying results of logistic regression analysis of independent predictors of stroke risk at 90 days and 7 days, respectively. In this study, both scores were tested in all groups except those in which the scores were originally derived. 2-day, 7-day, and 90-day risks of stroke were calculated by risk score. Areas under receiver-operator curves (c statistics) and 95% CIs were calculated as a measure of predictive ability. The c statistic integrates measures of sensitivity and specificity of the range of a variable. Ideal prediction produces a c statistic of 1·00, whereas prediction no better than chance is associated with a c statistic of 0·50. Statistical analyses were done with Stata (version 8, College Station, TX, USA).

Derivation and validation of a unified prognostic score

Each item included in either the California or ABCD prognostic score was evaluated as a potential component of a score that predicted risk of stroke within 2 days after TIA diagnosis in the original two derivation cohorts. All combinations of these components were used to generate potential risk scores by summing up the total number of weighted risk factors present for each patient, with the risk factor weighting schemes from each score tested individually. C statistics for these potential scores were then calculated and the score with the highest c statistic (best prediction) for 2-day risk prediction was selected.

The new prognostic score was tested in each of the validation cohorts. No alteration in the prognostic score was permitted after validation was initiated. Two-day, 7-day, and 90-day stroke risk was calculated by risk score, and c statistics and 95% confidence intervals were calculated. To provide a working estimate of stroke risk at each level of the risk score, summary risks were calculated at 2, 7, 30, and 90 days after TIA diagnosis by combining all six groups. The individual components of the risk score, including all risk factors identified in the previous two studies (all dichotomous), were then assessed by multivariable logistic regression analysis to confirm their importance to the score.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall, the two derivation groups and four validation groups included 4809 individuals with TIA (table 1) with evaluable data. The validation groups (n=2893) were generally similar to the derivation groups (n=1916). Non-white race, diabetes, and prolonged TIA were more frequent and atrial fibrillation less frequent in California than in Oxford.

Overall, strokes occurred in 442 patients (9·2%) within 90 days of presentation after TIA, 360 (7·5%) at 30 days, 267 (5·5%) at 7 days, and 189 (3·9%) at 2 days. In the six groups, 2-day risks of stroke varied from 1·7% to 4·9%, 7-day risks from 3·0% to 8·6%, and 90-day risks from 5·8% to 14·4% (table 2). Five of the 442 strokes (1·1%) were identified as haemorrhagic and all others were ischaemic. Strokes led to death within 90 days of the stroke in 90 patients (20%).

The California score generally predicted 2-day, 7-day, and 90-day risk of stroke well, with c statistics varying from 0·60 to 0·79 in the five groups that were not used to derive the score (table 2). Risks at each score value tended to be similar across the validation groups, and trends toward increased risk of stroke with higher scores were significant in every group. The ABCD score seemed to be a slightly better predictor of stroke risk than was the California score (c statistics from 0·62 to 0·81; table 3), although no significant differences were noted.

Since both previous prognostic scores validated well across a wide range of populations and contained several similar components, we generated a unified prognostic score for optimum prediction of 2-day risk. All combinations of individual components from the California and ABCD scores were used to create a series

	Derivation groups		Validation groups			
	California emergency department (n=1707)	Oxford population-based (n=209)*	California emergency department (n=1069)	California clinic (n=962)	Oxford population-based (n=547)	Oxford clinic (n=315)†
Group characteristics						
Location of population	San Francisco Bay Area	Oxfordshire, UK	San Francisco Bay Area	San Francisco Bay Area	Oxfordshire, UK	Oxfordshire, UK
Population size	2·6 million	105 000	2·7 million	2·7 million	91 106	500 000
Period	Mar 1997–Feb 1998	Jan 1981–Dec 1986	Mar 1998–Feb 1999	Mar 1998–Feb 1999	Apr 2002–Mar 2005	Apr 2002–Mar 2005
Location of initial ascertainment	16 emergency departments	10 family practices	16 emergency departments	16 primary care clinics	9 family practices	Hospital-based TIA clinic
Symptom onset to evaluation, median days (IQR)	0 (0–0)	1 (0–3)	0 (0–0)	1 (0–2)	0 (0–2)	1 (0–3)
Demographic characteristics, number (%)						
Age >60 years	1325 (78%)	167 (80%)	872 (80%)	722 (75%)	411 (75%)	208 (66%)
Female sex	899 (53%)	97 (46%)	559 (52%)	507 (53%)	300 (55%)	171 (54%)
White, non-Hispanic	1226 (80%)	206 (99%)	760 (70%)	671 (70%)	519 (95%)	296 (94%)
Medical history, number (%)						
Diabetes	332 (19%)	9 (4%)	210 (19%)	169 (18%)	49 (9%)	33 (10%)
Hypertension	988 (58%)	79 (38%)	619 (57%)	515 (54%)	233 (43%)	153 (50%)
Atrial fibrillation	151 (9%)	30 (14%)	78 (7%)	61 (6%)	61 (11%)	16 (5%)
Previous stroke	385 (23%)	0 (0%)		120 (12%)	63 (12%)	26 (8%)
Current cigarette smoking	200 (14%)	61 (29%)		169 (18%)	68 (12%)	63 (21%)
TIA symptoms, number (%)						
Duration 11–60 minutes	302 (18%)	62 (30%)	205 (19%)	153 (16%)	175 (32%)	101 (32%)
Duration >60 minutes	1139 (67%)	75 (37%)	779 (72%)	575 (60%)	274 (50%)	141 (45%)
Focal weakness	768 (45%)	112 (54%)	472 (44%)	322 (33%)	167 (31%)	112 (36%)
Change in speech	722 (42%)	82 (39%)	383 (35%)	245 (25%)	171 (31%)	113 (36%)
Examination findings, number (%)						
Systolic blood pressure >140 mm Hg	1281 (75%)	169 (81%)	857 (80%)	556 (60%)	297 (54%)	152 (48%)
Diastolic blood pressure >90 mm Hg	516 (30%)	103 (49%)	319 (30%)	262 (28%)	162 (30%)	90 (29%)
Management, number (%)						
Hospital admission	243 (14%)	12 (6%)	160 (15%)	31 (3%)	56 (10%)	14 (4%)
Aspirin	1154 (68%)	98 (47%)	735 (69%)	704 (73%)	451 (83%)	280 (89%)
Ticlopidine/clopidogrel	199 (12%)	0 (0%)	126 (12%)	84 (9%)	87 (16%)	19 (5%)
Anticoagulation	235 (14%)	11 (5%)	101 (9%)	64 (7%)	45 (8%)	12 (4%)
No antithrombotic therapy	143 (8%)	100 (48%)	165 (15%)	130 (14%)	32 (6%)	22 (7%)

*Data missing for duration of TIA symptoms in four patients and for blood pressure in three patients. †Data missing for duration of TIA symptoms in one patient and for blood pressure in two patients.

Table 1: **Characteristics of patients**

	Overall	California score						c statistic (95% CI)
		0	1	2	3	4	5	
Oxford population-based derivation group								
Patients	203	11	37	45	70	40	0	..
Stroke within 2 days	9 (4%)	0 (0%)	0 (0%)	2 (4%)	4 (6%)	3 (8%)	0	0·67 (0·52–0·81)
Stroke within 7 days	17 (9%)	0 (0%)	0 (0%)	4 (9%)	8 (11%)	5 (13%)	0	0·66 (0·55–0·77)
Stroke within 90 days	29 (14%)	0 (0%)	1 (3%)	7 (16%)	15 (21%)	6 (15%)	0	0·62 (0·53–0·71)
California emergency-department validation group								
Patients	1069	9	90	339	392	219	35	..
Stroke within 2 days	51 (5%)	0 (0%)	3 (3%)	11 (3%)	17 (4%)	18 (8%)	2 (6%)	0·60 (0·52–0·69)
Stroke within 7 days	71 (7%)	0 (0%)	4 (4%)	15 (4%)	26 (7%)	21 (10%)	5 (14%)	0·60 (0·54–0·67)
Stroke within 90 days	106 (10%)	0 (0%)	6 (7%)	18 (5%)	45 (11%)	30 (14%)	7 (20%)	0·61 (0·56–0·67)
California clinic validation group								
Patients	962	31	188	343	281	105	14	..
Stroke within 2 days	16 (2%)	0 (0%)	1 (1%)	2 (1%)	10 (4%)	3 (3%)	0	0·68 (0·58–0·79)
Stroke within 7 days	29 (3%)	0 (0%)	1 (1%)	4 (1%)	17 (6%)	7 (7%)	0 (0%)	0·72 (0·65–0·79)
Stroke within 90 days	56 (6%)	1 (3%)	6 (3%)	10 (3%)	28 (10%)	10 (10%)	1 (7%)	0·64 (0·57–0·71)
Oxford population-based validation group								
Patients	545	11	116	199	148	68	3	..
Stroke within 2 days	20 (4%)	0 (0%)	1 (1%)	2 (1%)	10 (7%)	6 (9%)	1 (33%)	0·75 (0·66–0·85)
Stroke within 7 days	29 (5%)	0 (0%)	1 (1%)	2 (1%)	14 (9%)	11 (16%)	1 (33%)	0·79 (0·72–0·87)
Stroke within 90 days	48 (9%)	1 (9%)	2 (2%)	8 (4%)	22 (15%)	14 (21%)	1 (33%)	0·72 (0·65–0·80)
Oxford clinic validation group								
Patients	315	20	53	117	83	38	4	..
Stroke within 2 days	9 (3%)	0 (0%)	0 (0%)	2 (2%)	4 (5%)	2 (5%)	1 (25%)	0·74 (0·60–0·88)
Stroke within 7 days	17 (5%)	0 (0%)	0 (0%)	5 (4%)	8 (10%)	3 (8%)	1 (25%)	0·70 (0·60–0·81)
Stroke within 90 days	22 (7%)	0 (0%)	0 (0%)	5 (4%)	12 (14%)	3 (8%)	2 (50%)	0·73 (0·64–0·82)

Data are number or number (%), unless otherwise stated.

Table 2: **2-day, 7-day, and 90-day risk of stroke by California score**

of simple scores, which were then tested in multivariable models predicting 2-day risk. In both derivation groups, the score with the greatest c statistic was one that scored points for each of five factors: age 60 years or older (1 point); blood pressure elevation on first assessment after TIA (1 point; systolic ≥140 mm Hg or diastolic ≥90 mm Hg); clinical features of TIA (unilateral weakness, 2 points; or speech impairment without weakness, 1 point); duration of TIA (≥60 minutes, 2 points; or 10–59 minutes, 1 point); and diabetes (1 point). This was also the score that predicted stroke risk best when data from the two derivation groups were combined. We termed this the ABCD² score, on the basis of the initials of the five factors (Age, Blood pressure, Clinical features, Duration, Diabetes).

Each individual in the four validation groups was classified according to the ABCD² score (table 4). In these four groups, 2-day stroke risk was 0% for an ABCD² score of 0 or 1, 1–2% for a score of 2, 0–3% for 3, 2–5% for 4, 3–7% for 5, 4–14% for 6, and 0–50% for 7. For the ABCD² score, c statistics varied from 0·62 to 0·83 in the four validation groups and were generally higher than for California or ABCD scores, although the 95% CI overlapped (tables 2–4). Similar to 2-day risks of stroke, 7-day and 90-day risks tended to be greater with higher ABCD² scores than with lower scores (table 4).

In view of the similar patterns and absolute stroke risks for ABCD² scores across the four validation and two derivation cohorts, we combined them to obtain a working estimate of stroke risk at each level of the ABCD² score (figure). Similar to results for 2-day, 7-day, and 90–day risks of stroke, risk at 30 days after TIA diagnosis also generally rose with increased scores. Overall, 47 of 4799 (1%) patients with complete information in the combined cohorts scored 0, 191 (4%) scored 1, 543 (11%) scored 2, 847 (18%) scored 3, 1165 (24%) scored 4, 994 (21%) scored 5, 852 (18%) scored 6, and 160 (3%) scored 7 (table 4).

Of 3735 patients from the four Californian groups with race coded in detail, the score predicted 2-day risk of stroke similarly in patients who were white (c statistic 0·68, 95% CI 0·63–0·72), African-American (0·59, 0·46–0·71), Asian-American (0·64, 0·46–0·82), and Hispanic (0·72, 0·59–0·85). The proportion of non-white patients was too low in the Oxford groups to allow

separate analysis. In the subset of Californian patients for whom we had a neurologist's review of the TIA (n=1707), the c statistic for individuals with a neurologist-confirmed diagnosis of TIA (n=1429, c statistic 0·66, 95% CI 0·60–0·72) was similar to that of those thought not to have TIA after neurologist review (n=278, 0·73, 0·53–0·93). In the Oxford groups, there was no difference in the predictive power of the score between patients with a confirmed diagnosis of TIA (n=690, c statistic 0·80, 95% CI 0·71–0·89) and those subsequently thought not to have had a TIA (n=381, 0·74, 0·55–0·92).

We grouped scores to create strata for low, moderate, and high risk, with a goal of identifying patients who could be managed non-urgently and those who probably need priority evaluation, treatment, and observation. Overall, 1628 (34%) were classified as low risk, defined as a score of less than 4 (stroke risk 1·0% at 2 days, 1·2% at 7 days, and 3·1% at 90 days), 2169 (45%) as moderate risk with a score of 4 or 5 (stroke risk 4·1% at 2 days, 5·9% at 7 days, and 9·8% at 90 days), and 1012 (21%) as high risk with a score of greater than 5 (stroke risk 8·1% at 2 days, 11·7% at 7 days, and 17·8% at 90 days).

Of 4746 patients who did not have a stroke during the emergency department evaluation for TIA, 432 (9·1%) were admitted to hospital for the initial attack, mainly in California. Overall, 111 (85%) of 130 strokes occurring within 2 days of the TIA were in patients who were not admitted to hospital, and 45 of these 111 (41%) had an ABCD² score of greater than 5. A policy dictating admission for those at high risk and no admission for those at low risk (with current admission practices applied to those with moderate risk) would have resulted in hospital admission for 1101 (23%), and 67 (52%) of strokes would have occurred in those not admitted. A policy dictating admission for all those with moderate or greater risk would have resulted in 3124 admissions (66%), and 11 (9%) of strokes would have occurred in those not admitted.

All the components of the ABCD² score were predictors of stroke at 90 days in multivariable analysis of the combined cohorts, with coefficients of similar magnitude for predictions at 2, 7, and 90 days, and weightings generally supporting those used in the score (table 5), further justifying the unified score.

	Overall	ABCD score							c statistic (95% CI)
		0	1	2	3	4	5	6	
California emergency department derivation group									
Patients	1707	6	45	161	282	478	395	340	
Stroke within 2 days	83 (5%)	0 (0%)	0 (0%)	3 (2%)	6 (2%)	20 (4%)	28 (7%)	26 (8%)	0·64 (0·59–0·69)
Stroke within 7 days	103 (6%)	0 (0%)	0 (0%)	3 (2%)	7 (2%)	26 (5%)	34 (9%)	33 (10%)	0·65 (0·60–0·70)
Stroke within 90 days	180 (11)	0 (0%)	1 (2%)	6 (4%)	12 (4%)	47 (10%)	54(14%)	60 (18%)	0·65 (0·61–0·69)
California emergency department validation group									
Patients	1069	2	19	82	190	269	250	257	
Stroke within 2 days	51 (5%)	0 (0%)	0 (0%)	3 (4%)	5 (3%)	9 (3%)	13 (5%)	21 (8%)	0·62 (0·55–0·70)
Stroke within 7 days	71 (7%)	0 (0%)	0 (0%)	4 (5%)	5 (3%)	14 (5%)	19 (8%)	29 (11%)	0·64 (0·57–0·70)
Stroke within 90 days	106 (10%)	0 (0%)	0 (0%)	6 (7%)	10 (5%)	20 (7%)	27 (11%)	43 (17%)	0·63 (0·58–0·68)
California clinic validation group									
Patients	962	17	73	157	212	250	140	113	
Stroke within 2 days	16 (2%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	6 (2%)	5 (4%)	4 (4%)	0·72 (0·61–0·83)
Stroke within 7 days	29 (3%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	8 (3%)	11 (8%)	8 (7%)	0·76 (0·68–0·83)
Stroke within 90 days	56 (6%)	0 (0%)	3 (4%)	2 (1%)	7 (3%)	14 (6%)	16 (11%)	14 (12%)	0·69 (0·62–0·75)
Oxford population-based validation group									
Patients	543	5	40	107	124	125	92	50	
Stroke within 2 days	20 (4%)	0 (0%)	0 (0%)	2 (2%)	1 (1%)	3 (2%)	7 (8%)	7 (14%)	0·76 (0·65–0·87)
Stroke within 7 days	29 (5%)	0 (0%)	0 (0%)	2 (2%)	1 (1%)	4 (3%)	9(10%)	13 (26%)	0·81 (0·73–0·89)
Stroke within 90 days	48 (9%)	0 (0%)	1 (3%)	4 (4%)	4 (3%)	10 (8%)	14(15%)	15 (30%)	0·74 (0·66–0·81)
Oxford clinic validation group									
Patients	315	15	22	58	72	75	49	24	
Stroke within 2 days	9 (3%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	3 (4%)	3 (6%)	2 (8%)	0·72 (0·55–0·91)
Stroke within 7 days	17 (5%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	8 (11%)	4 (8%)	4 (17%)	0·75 (0·64–0·86)
Stroke within 90 days	22 (7%)	0 (0%)	1 (5%)	0 (0%)	1 (1%)	8 (11%)	7(14%)	5 (21%)	0·77 (0·67–0·86)

Data are number or number (%), unless otherwise stated.

Table 3: **2-day, 7-day, and 90-day risk of stroke by ABCD score.**

	Overall	ABCD² score								c statistic (95% CI)
		0	1	2	3	4	5	6	7	
California emergency department derivation group										
Patients	1707	6	39	143	262	429	395	361	72	
Stroke within 2 days	83 (5%)	0 (0%)	0 (0%)	2 (1%)	4 (2%)	19 (4%)	21 (5%)	31 (9%)	6 (8%)	0·66 (0·60–0·71)
Stroke within 7 days	103 (6%)	0 (0%)	0 (0%)	2 (1%)	4 (2%)	25 (6%)	25 (6%)	40 (11%)	7 (10%)	0·66 (0·62–0·71)
Stroke within 90 days	180 (11%)	0 (0%)	1 (3%)	5 (3%)	8 (3%)	37 (9%)	49 (12%)	62 (17%)	18 (25%)	0·67 (0·63–0·71)
Oxford population-based derivation group										
Patients	203	4	14	27	25	43	54	36	0	
Stroke within 2 days	9 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)	4 (7%)	3 (8%)	0 (0%)	0·72 (0·60–0·84)
Stroke within 7 days	17 (9%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	3 (7%)	7 (13%)	6 (17%)	0 (0%)	0·72 (0·62–0·82)
Stroke within 90 days	29 (14%)	0 (0%)	0 (0%)	0 (0%)	3 (12%)	7 (16%)	10 (19%)	9 (25%)	0 (0%)	0·69 (0·60–0·77)
California emergency department validation group										
Patients	1069	2	16	65	176	259	247	247	57	
Stroke within 2 days	51 (5%)	0 (0%)	0 (0%)	1 (2%)	6 (3%)	9 (3%)	11 (4%)	21 (9%)	3 (5%)	0·62 (0·54–0·69)
Stroke within 7 days	71 (7%)	0 (0%)	0 (0%)	2 (3%)	6 (3%)	14 (5%)	16 (6%)	26 (11%)	7 (12%)	0·63 (0·57–0·69)
Stroke within 90 days	106 (10%)	0 (0%)	0 (0%)	4 (6%)	8 (5%)	20 (8%)	25 (10%)	39 16%)	10 (18%)	0·64 (0·58–0·69)
California clinic validation group										
Patients	962	15	65	148	198	230	167	113	26	
Stroke within 2 days	16 (2%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	5 (2%)	5 (3%)	5 (4%)	0 (0%)	0·72 (0·61–0·82)
Stroke within 7 days	29 (3%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	6 (3%)	11 (7%)	8 (7%)	2 (8%)	0·75 (0·68–0·83)
Stroke within 90 days	56 (6%)	0 (0%)	2 (3%)	3 (2%)	6 (3%)	12 (5%)	16 (10%)	12 (11%)	5 (19%)	0·68 (0·61–0·75)
Oxford population-based validation group										
Patients	543	5	38	102	116	133	83	64	2	
Stroke within 2 days	20 (4%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	3 (2%)	5 (6%)	9 (14%)	1 (50%)	0·79 (0·68–0·90)
Stroke within 7 days	29 (5%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	4 (3%)	6 (7%)	16 (25%)	1 (50%)	0·83 (0·75–0·91)
Stroke within 90 days	48 (9%)	0 (0%)	1 (3%)	4 (4%)	3 (3%)	9 (7%)	12 (14%)	18 (28%)	1 (50%)	0·75 (0·67–0·82)
Oxford clinic validation group										
Patients	315	15	19	58	70	71	48	31	3	
Stroke within 2 days	9 (3%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	3 (4%)	2 (4%)	3 (10%)	0 (0%)	0·73 (0·57–0·89)
Stroke within 7 days	17 (5%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	8 (11%)	3 (6%)	5 (16%)	0 (0%)	0·74 (0·64–0·84)
Stroke within 90 days	22 (7%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)	8 (11%)	6 (13%)	5 (16%)	1 (33%)	0·75 (0·67–0·84)

Data are number or number (%), unless otherwise stated.

Table 4: **2-day, 7-day, and 90-day risk of stroke by ABCD² score**

Discussion

The California score and the ABCD score both reliably predicted short-term risk of stroke after presentation with TIA. They were derived in different populations of patients and for prediction of stroke at different time points, but contained similar components. Both scores predicted stroke risk reliably in independent groups from distinct regions, in patients seen in emergency departments and outpatient clinics, and in population-based and hospital-based groups. In view of the similarities in the two prognostic scores and the need to define a score optimised to predict very acute risk, we created a unified score for predicting 2-day risk of stroke, to serve as a standard for clinical care and public education.

The new score, termed ABCD², was a more accurate predictor than either of the previous scores in the two derivation groups and generally performed better in the four validation cohorts. Although 95% CI for c statistics with the various scores overlapped, an analysis in which all groups were combined showed that each element of ABCD² was an independent predictor of stroke risk at 90 days, with similar sized coefficients at 2 days and 7 days, justifying inclusion of all of these factors in the unified score (table 5). In 4799 patients with complete data in the combined validation groups, the 2-day risk of stroke was 1·0% with a score of zero to three (low risk), 4·1% with four or five (moderate risk), and 8·1% with six or seven (high risk), and the score divided the population well. Similarly, the score predicted stroke risks well at time points varying from 7 days to 90 days after presentation with symptoms of TIA.

The overall short-term risk of stroke after TIA in the combined groups was slightly lower than in some previous studies. To reflect how the score would actually be used in clinical practice, events were counted from the time of presentation rather than symptom onset, and some strokes occurring after TIA but before

presentation would have been missed. Nonetheless, the overall stroke risks of 3·9% at 2 days, 5·5% at 7 days, and 9·2% at 90 days are substantial. In patients presenting with chest pain, a population often treated urgently and observed for 24 h in the hospital, short-term risks of myocardial infarction and major cardiovascular complications are comparable to, or lower than, that of stroke after TIA.[18–20]

Recommended acute approaches in patients with TIA include brain imaging, carotid imaging, antiplatelet therapy, and statins.[11,12] Urgent carotid imaging might be especially pertinent because endarterectomy for patients with substantial symptomatic carotid stenosis is more effective if done early,[21] presumably because early surgery reduces the high risk of stroke immediately after presentation with symptoms. Recommendations on hospital admission have been vague, and practice varies greatly.[13] Some interventions after TIA are expensive[9,22] and might not be cost effective if used in all patients. The ABCD² score might be useful in determining which patients are admitted and which need assessment within 24 h. Based on results of a previous cost-utility analysis,[10] an ABCD² score of 4 or greater might justify 24-h admission in the USA solely on the basis of a greater opportunity to administer thrombolysis early if a subsequent stroke occurs in the hospital as opposed to at home. Specific cutpoints prompting aggressive interventions are likely to vary between settings and regions, and between interventions, but the 21% of patients classified as high risk (score >5) are likely to benefit from urgent evaluation, treatment, and observation in most developed health-care systems, particularly in view of the great cost of stroke. On the other hand, most patients with a score of less than 4 will not need hospital observation. For the intermediate group with scores of 4 or 5, the risk of stroke is substantial, but characteristics of the individual patient and constraints of the health-care system are likely to be more important in determining the necessity of observation. Similar criteria could be applied to stratify risk in patients with carotid disease in health-care systems where timely access to carotid surgery cannot be provided for all endarterectomy candidates. Practice varies greatly worldwide, so use of the score could either increase or decrease rates of admission in particular countries.

Other studies have assessed clinical predictors of stroke in the first weeks after a TIA. Some findings have confirmed the presence of weakness,[6,23] older age,[24] and diabetes[24] as risk factors for stroke after TIA, whereas others have not.[7] None of these studies has attempted to create prognostic scores for stroke after TIA, and most are small or based on administrative data. Two small published studies have attempted to validate the ABCD score[15,25] One study, based on 22 stroke outcomes, showed very good predictive power (c-statistic 0·78, 95% CI 0·69–0·87),[15] but the second study had only two stroke outcomes during follow-up and was therefore underpowered.[25] Our present study included several diverse validation groups and should establish a high

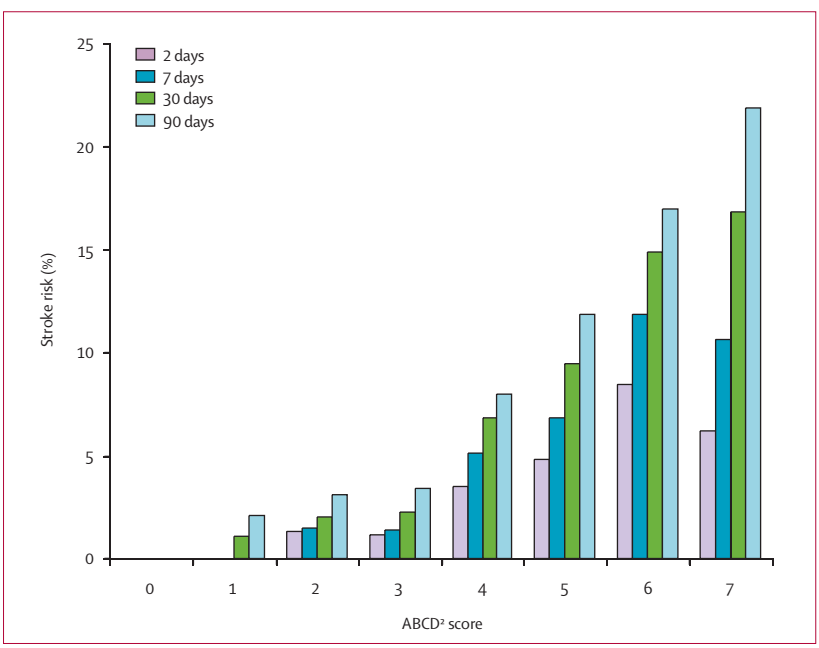

Figure: **Short-term risk of stroke by ABCD² score in six groups combined (n=4799)**

	Number (%), n=4809	2-day risk		7-day risk		90-day risk	
		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age >60 years	3690 (77%)	1·4 (1·0–2·1)	0·07	1·4 (1·0–2·0)	0·040	1·5 (1·2–2·0)	0·002
Diabetes mellitus	797 (17%)	1·6 (1·1–2·2)	0·01	1·4 (1·1–1·9)	0·017	1·7 (1·3–2·1)	<0·0001
SBP >140 mm Hg or DBP >90 mm Hg	3420 (71%)	2·1 (1·4–3·1)	0·0003	1·9 (1·4–2·6)	<0·001	1·6 (1·2–2·0)	0·0003
Duration 10–59 minutes vs <10 minutes	993 (21%)	2·0 (1·0–3·7)	0·04	1·9 (1·1–3·3)	0·032	1·7 (1·1–2·5)	0·02
Duration >60 minutes vs <10 minutes	2973 (62%)	2·3 (1·3–4·0)	0·004	2·6 (1·6–4·3)	<0·001	2·1 (1·5–3·0)	<0·0001
Speech impairment without focal weakness	899 (19%)	1·4 (0·8–2·3)	0·2	1·5 (1·0–2·4)	0·065	1·7 (1·2–2·3)	0·002
Focal weakness	1979 (41%)	2·9 (2·0–4·3)	<0·0001	3·5 (2·5–4·8)	<0·001	3·2 (2·5–4·1)	<0·0001

All listed independent predictors were included in logistic regression analysis. SBP=systolic blood pressure. DBP=diastolic blood pressure.

Table 5: **Predictors from multivariable models of stroke at 2 days, 7 days, and 90 days after TIA in the six groups combined**

standard of validation. Of course, it will be reassuring to see additional validations in large groups from additional populations and health-care systems.

The ABCD² score might predict risk of stroke partly because it identifies patients more likely to have had a true TIA. The diagnosis of TIA is unreliable;[26,27] transient neurological symptoms due to seizure, migraine, or syncope may be indistinguishable from those due to focal brain or retinal ischaemia.[28] Spells of longer duration and those accompanied by focal weakness might be more likely to represent true TIAs, as suggested by findings showing a higher prevalence of new ischaemic brain lesions in patients with clinical TIAs who have these characteristics.[29–31] Incidence of cerebral ischaemia increases with age and in patients with diabetes, and in some studies, diabetes is also associated with an increased likelihood of finding new ischaemia in brain imaging of patients with TIA.[30,31] Individuals with raised blood pressure on initial evaluation might be more likely to have uncontrolled hypertension. In fact, the frequency of acute ischaemic lesions on diffusion weighted MRI in patients with TIA increased with the original ABCD score.[32] Since the score might work in part because it identifies true TIAs, it should not supersede expert neurological judgement.

Diagnostic studies could enhance prediction of stroke risk after TIA. The presence of new ischaemic lesions on MRI scan or head CT in patients with transient symptoms can portend an increased short-term risk of stroke,[33–35] and clinical risk scores and imaging results can be independent predictors when both are included in models predicting stroke risk.[15,33] Large-vessel cervicocerebral occlusion on imaging might also be associated with greater risk,[34–36] and embolic signals on transcranial Doppler sonography are associated with short-term risk of stroke.[37,38] Since the simple clinical criteria in the ABCD² score are associated with imaging findings,[29,32] it is unclear whether brain and vascular imaging would enhance the predictability of the ABCD² score. In view of the imperfect prediction of the score, further research on imaging and other potential biomarkers is justified. Also, it should be recognised that brain and vascular imaging is recommended for all patients with TIA to identify causes and target efforts to prevent stroke.[12]

This study has several limitations. First, although most patients included in our groups presented within 1 day of TIA, some did not. Since rates of stroke are especially high during the first few days after TIA and fall thereafter,[3] the overall risks of stroke would be expected to be lower in those presenting later after TIA and the ABCD² score might not be as useful then. Second, the score was applied to all patients with an initial diagnosis of TIA. Neurologists might make more accurate diagnoses than do other health-care practitioners and this difference could reduce the usefulness of the score. However, when the groups were limited to those with neurologist-confirmed TIAs, the ABCD² score remained highly predictive. Third, we did not attempt to integrate information from diagnostic assessments, which could have increased the predictive power of a prognostic score. However, such assessments vary greatly, and the ABCD² score can be applied easily and could guide subsequent evaluation. Fourth, treatment variables were not considered in creating or validating the scores. However, accounting for such variables would not be expected to weaken the association of the score with outcome unless patients at low risk were preferentially selected for treatment. Fifth, some data were gathered retrospectively in the California cohorts, particularly the characteristics of the TIA. Data were obtained without knowledge of subsequent events, however, so this method would tend to underestimate the true predictive capacity of the score. Moreover, all the data in the Oxford population-based groups were obtained by prospective face-to-face assessment of patients in the acute phase after TIA by the authors or other study neurologists as part of the daily clinical service. Sixth, the generalisability of observations made on emergency department cohorts to the broader population of patients with TIA could be questioned. However, the scores were similarly predictive in a cohort of patients presenting to clinics in California and in the two Oxford population-based studies, which had near complete ascertainment of all patients presenting with TIA. Finally, c statistics of the ABCD² score tended to be greater than those of the previous scores, but the differences were not significant. However, the addition of diabetes to the ABCD score is justified on the basis that it has significant independent predictive power, as was also noted in a pooled analysis of the two population-based Oxford groups in the publication that originally described the score.[14] Diabetes was also found to be an independent predictor of 30-day stroke risk in another study.[15] Use of a sole standard score will reduce confusion and should increase implementation.

The ABCD² score might also be useful for educating the public. Overall, public knowledge about TIA, including its definition, typical symptoms, and appropriate action, is very limited.[39,40] Although it might be best to recommend prompt evaluation for any neurological symptoms of sudden onset, whether they resolve or not, the ABCD² score will allow the presenting characteristics associated with highest early risk of stroke to be emphasised.

Findings of many studies have confirmed that the short-term risk of stroke is raised after TIA.[1,3–8] The ABCD² score allows identification of groups at especially high risk, in whom aggressive evaluation and urgent intervention is clearly justified. Potential interventions include observation to increase likelihood of delivering tissue plasminogen activator rapidly in case of subsequent stroke, but no specific treatment has been reliably assessed in any large-scale trials in the acute

phase after TIA.[41] However, many treatments, such as antiplatelet agents and statins in the acute phase and timely endarterectomy for severe carotid stenosis, are very likely to be beneficial, and so randomisation to placebo is not feasible. For such interventions, the key question is therefore to what extent the absolute benefits (and risks) of treatment are increased by earlier intervention? The EXPRESS study[41,42] should provide the necessary data later this year, with benefit of early intervention stratified by ABCD² score. However, because of the very high risks of stroke in identifiable subgroups of patients with TIA, which are generally greater than those of myocardial infarction in patients with chest pain, randomised trials of new treatments are also urgently needed.

Acknowledgments

We thank Barbara Rowe, Michael Sorel, and Ziyah Mehta for careful analysis. This work was funded by the NIH/NINDS (NS 02042); a Grant-in-Aid from the American Heart Association, Western States Affiliate; the UK Stroke Association; the BUPA Foundation; and the UK Medical Research Council.

Conflict of interest statement

We declare that we have no conflict of interest.

Contributors

S C Johnston and P M Rothwell had the idea for the study and, with M F Giles and S Sidney, did the analyses. M Nguyen-Huynh, J S Elkins, and A L Bernstein adjudicated outcomes in the primary data from the California studies. All authors contributed to the writing of the report.

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