Prospective validation of Canadian TIA Score and comparison with ABCD2 and ABCD2i for subsequent stroke risk after transient ischaemic attack: multicentre prospective cohort study

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ABSTRACT

OBJECTIVE

To validate the previously derived Canadian TIA Score to stratify subsequent stroke risk in a new cohort of emergency department patients with transient ischaemic attack.

DESIGN

Prospective cohort study.

SETTING

13 Canadian emergency departments over five years.

PARTICIPANTS

7607 consecutively enrolled adult patients attending the emergency department with transient ischaemic attack or minor stroke.

MAIN OUTCOME MEASURES

The primary outcome was subsequent stroke or carotid endarterectomy/carotid artery stenting within seven days. The secondary outcome was subsequent stroke within seven days (with or without carotid endarterectomy/carotid artery stenting). Telephone follow-up used the validated Questionnaire for Verifying Stroke Free Status at seven and 90 days. All outcomes were adjudicated by panels of three stroke experts, blinded to the index emergency department visit.

RESULTS

Of the 7607 patients, 108 (1.4%) had a subsequent stroke within seven days, 83 (1.1%) had carotid endarterectomy/carotid artery stenting within seven days, and nine had both. The Canadian TIA Score stratified the risk of stroke, carotid endarterectomy/carotid artery stenting, or both within seven days as low (risk ≤0.5%; interval likelihood ratio 0.20, 95% confidence interval 0.09 to 0.44), medium (risk 2.3%; interval likelihood ratio 0.94, 0.85 to 1.04), and high (risk 5.9% interval likelihood ratio 2.56, 2.02 to 3.25) more accurately (area under the curve 0.70, 95% confidence interval 0.66 to 0.73) than did the ABCD2 (0.60, 0.55 to 0.64) or ABCD2i (0.64, 0.59 to 0.68). Results were similar for subsequent stroke regardless of carotid endarterectomy/carotid artery stenting within seven days.

CONCLUSION

The Canadian TIA Score stratifies patients' seven day risk for stroke, with or without carotid endarterectomy/carotid artery stenting, and is now ready for clinical use. Incorporating this validated risk estimate into management plans should improve early decision making at the index emergency visit regarding benefits of hospital admission, timing of investigations, and prioritisation of specialist referral.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients with transient ischaemic attack are at heightened risk for a subsequent major stroke or death, especially within the first few days

Optimising stroke prevention requires more precise risk stratification than existing tools can offer, to minimise both under-treatment and over-treatment

WHAT THIS STUDY ADDS

After transient ischaemic attack, the Canadian TIA Score outperformed other tools to stratify seven day risk of stroke, with or without carotid interventions

Incorporating this now validated core into management plans at the index emergency visit should improve early decision making on hospital admission, timing of investigations, and specialist referral

Introduction

Patients who have a transient ischaemic attack are at high risk of a subsequent stroke, especially in the short term. Historically, studies have estimated the overall risk of stroke to be 4-10% within seven days of transient ischaemic attack, increasing to 8-12% by 90 days.[1-9] However, the management of transient ischaemic attacks has changed markedly in the past decade,[4 10 11] and much lower subsequent stroke rates are attainable.[4-9 12] Importantly, most of the subsequent risk of stroke is in the first days after the index visit.[4 9] Nevertheless, comprehensive investigation, aggressive treatment, and/or hospital admission for all patients who present to the emergency department with symptoms suggestive of a transient ischaemic attack is both inefficient and challenging for most health systems, so prioritising care to those most likely to benefit is essential. Likewise, the ability to identify patients at very low risk benefits both providers and patients.

Clinical decision rules or scores derived from original research help clinicians with diagnostic or therapeutic decisions at the bedside but need to be validated before implementation.[13-15] The best known score for triage of transient ischaemic attack is the ABCD2 score. However, this instrument has not been able to discriminate particularly well between

groups at low and high risk during prospective validation.[16-19] Several variations of the ABCD2 score are now available, which include neuroimaging, recent previous transient ischaemic attack, and vascular imaging.[20] These scores are typically used to dichotomise risk as low versus high. Our study team previously prospectively derived the Canadian TIA Score (table 1) from nearly 4000 patients prospectively enrolled at eight large Canadian hospital emergency departments.[21] This score incorporates 13 predictive variables from history, physical examination, and testing routinely performed at the time of presentation to the emergency department. The assigned score, which ranges from −3 to 23, can be used to assign a graded probability of stroke in the subsequent week ranging from 0.01% to 28%. Alternatively, it can be grouped into three risk levels—namely, low, medium, and high risk—to prioritise investigations, admission, and follow-up in specialty clinics at the time of the index emergency department visit. Therefore, to ensure that this score can be safely introduced into clinical practice, our objective was to validate the previously derived Canadian TIA Score to stratify subsequent risk of stroke in a new cohort of emergency department patients and to compare it with existing risk stratification scores.

Methods

Study population and setting

We conducted a prospective multicentre cohort study at 13 Canadian emergency departments (10 university affiliated tertiary care hospitals and three urban community hospitals), including six sites (two community, four university) not involved in the original derivation study. We enrolled patients over a five year period from 31 October 2012 to 30 May 2017.

We prospectively enrolled consecutive patients attending the emergency department seven days a week, 24 hours a day at all sites. Patients were aged 18 years or older, with transient ischaemic attack or minor stroke as their final emergency department diagnosis at the time of discharge or specialist consultation. We excluded patients who had neurological deficits for more than 24 hours (that is, a stroke according to the World Health Organization's definition), had a decreased level of consciousness from their baseline (that is, Glasgow Coma Scale <15 in previously cognitively normal patients), had an alternative diagnosis (for example, hypoglycaemia, seizure, electrolyte imbalance, or migraine), presented more than seven days after onset of the neurological symptoms, or were treated with tissue plasminogen activator or embolectomy for an acute stroke.

Table 1 | Canadian TIA Score

Items	Points
Clinical findings:	
1) First transient ischaemic attack (in lifetime)	2
2) Symptoms ≥10 minutes	2
3) Past history of carotid stenosis	2
4) Already on antiplatelet therapy	3
5) History of gait disturbance	1
6) History of unilateral weakness	1
7) History of vertigo	−3
8) Initial triage diastolic blood pressure ≥110 mm Hg	3
9) Dysarthria or aphasia (history or examination)	1
Investigations in emergency department:	
1) Atrial fibrillation on electrocardiogram	2
2) Infarction (new or old) on computed tomography	1
3) Platelet count ≥400×10^9/L	2
4) Glucose ≥15 mmol/L	3
Total score (−3 to 23):	X

Data collection

Attending emergency physicians, neurologists, or supervised resident physicians completed all assessments. Physicians were oriented to the study and the standardised data collection forms by means of a formal one hour lecture, as well as individual orientation of the study forms including definitions and procedures by local study staff. Physicians completed data forms to explicitly record each element of the Canadian TIA Score, the ABCD2 score, and the ABCD2i score (ABCD2 score plus 3 points for infarction on neuroimaging).

Study personnel collected data forms, verified data, confirmed eligibility, and recorded non-subjective data (for example, age, triage vital signs, laboratory results) from review of all medical records, including those from physicians, nurses, consultants, emergency medical services, follow-up neurological consultations, discharge summaries, and laboratory and radiology reports. We searched the study hospital's electronic medical records to identify subsequent emergency department visits, stroke/neurology clinic visits, and diagnostic imaging. We conducted telephone follow-up calls at seven and 90 days for patients not in hospital at these time points, to assess for subsequent stroke or subsequent transient ischaemic attacks, using the previously validated Questionnaire for Verifying Stroke Free Status.[22 23] In addition to this questionnaire, we asked patients whether they had been admitted for stroke subsequent to their initial emergency department visit and whether they experienced subsequent neurological deficits and, if so, the duration, the date of onset, and the side(s) affected. We have successfully used the same proxy outcome method in previous work.[24]

Study nurses reviewed all emergency department visits during the study period to identify any missed and potentially eligible patients. If such patients were not clearly ineligible on the basis of review of medical record, they were deemed to be missed eligible patients, and their characteristics were abstracted onto a standardised data collection form for missed eligible patients. Data management and study coordination were conducted at the Ottawa Hospital Research Institute.

Outcome measures

The primary outcome was the composite of subsequent stroke or carotid revascularisation (that is, carotid endarterectomy or carotid artery stenting) within seven

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days of the index emergency department visit. We defined subsequent stroke as new, rapidly developing clinical symptom(s) of focal (or occasionally global) disturbance of cerebral function lasting more than 24 hours or until death, with no apparent non-vascular cause.[25] As a secondary outcome, we examined only subsequent stroke within seven days of the emergency department diagnosis of transient ischaemic attack, regardless of carotid revascularisation.

Outcome assessment

We assessed the outcomes for all patients, incorporating data from all possible sources including site hospital records for stroke occurrence, admission, or mortality; autopsy report at the site hospital; or patients answering "yes" to one or more of the telephone follow-up questions. Local adjudication committees, blinded to the initial emergency department visit (that is, study form and physician and nursing notes before a possible subsequent event), reviewed all possible outcomes. The adjudication committees were composed of two stroke neurologists and one experienced emergency physician (two sites used two experienced emergency physicians and one stroke neurologist). These assessors independently assessed each possible outcome, and every outcome event required majority agreement.

Data analyses

We calculated the classification performance of the Canadian TIA Score for each risk category (low, medium, and high) by using interval likelihood ratios with 95% confidence intervals. The interval likelihood ratio is the multilevel extension of the positive and negative likelihood ratios, which are applicable only when a test/risk score is dichotomised into two levels (positive versus negative or high risk versus low risk). We pre-specified risk thresholds (low risk <1%, medium risk 1-5%, and high risk >5%) on the basis of previous surveys of emergency physicians and neurologists to group discrete risk scores into these three risk levels.[26 27] We calculated the sensitivity and specificity when the score was dichotomised at each integer value from −3 to 23. We also assessed the classification of the ABCD2 and ABCD2i scores for both the primary and secondary outcomes according to their ability to classify patients as being at low, medium, and high risk using cut-off points based on the same risk thresholds (low risk <1%, medium risk 1-5%, and high risk >5%). We also compared the C statistic (area under the curve) by using the discrete values for each score. We used the DeLong method to test for the significance of these differences. We also calculated the absolute net reclassification indices by using three levels (low, medium, and high risk) comparing the Canadian TIA Score with the ABCD2 and ABCD2i scores. Sample size was based on estimation of the precision of the classification performance of the risk scale. Our goal was to enrol enough subsequent patients with stroke to be able to evaluate the sensitivity with 95% confidence bands plus/minus 10%, corresponding to 90 subsequent stroke cases. From our previous study, in which 2.2% of eligible patients had a stroke within seven days of their diagnosis of transient ischaemic attack, we estimated that we would need a sample size of 5000 patients with transient ischaemic attack.

With the increasing use of prompt emergency carotid endarterectomy at study sites during the accrual phase of this study, and its potentially large effect on short term stroke (that is, an estimated number needed to treat to avert stroke or death of 3.3[28]), our primary outcome was altered from our previous derivation study to become the composite of either subsequent stroke or carotid endarterectomy/carotid artery stenting within seven days. Although we expected this change to increase the primary outcome event rate, we maintained the original study sample size target of 90 stroke events (with or without carotid endarterectomy/carotid artery stenting), which we designated as our secondary outcome of interest.

Patient and public involvement

Neither patients nor the public were formally involved in the planning of the study. We plan to involve patients before assessing the effects of implementing this rule in clinical practice.

Results

We enrolled 7607 patients, representing 80.6% of all potentially eligible patients seen at the participating emergency departments during the study period. Follow-up by telephone, clinic assessment, or both was almost complete, with only 34 (0.4%) patients lost to follow-up by seven days (that is, not reached by telephone and no subsequent hospital encounters). One hundred and eight (1.4%) patients had a subsequent stroke and 83 (1.1%) had carotid revascularisation within seven days of their index visit (total of 182 outcomes, as nine patients had both). Missed patients who were not enrolled were similar to enrolled patients with regards to age, sex, and diagnostic testing but were admitted to hospital more often (18.4% *v* 5.8%) (appendix 1).

Table 2 shows the clinical features of our cohort. The patients had a mean age of 68.5 years, and 52.3% were women; three quarters reported this being their first transient ischaemic attack. The most common presenting symptoms were sensory deficits, weakness, and speech difficulties. More than a third of patients arrived by ambulance, and half had had symptoms for more than an hour. Almost all patients had computed tomography of the head (96.5%) and electrocardiography (91.0%). Most patients either continued or started taking aspirin, clopidogrel, or both. Very few patients (5.8%) were admitted to hospital from the emergency department at the time of their index visit.

The Canadian TIA score was able to risk stratify patients into the three risk groups efficiently (table 3), with about one in six patients found to be at low risk (<1% risk for the primary outcome; interval likelihood ratio 0.20, 95% confidence interval 0.09 to 0.44), and

Table 2 | Clinical characteristics of 7607 patients with transient ischaemic attack (TIA) admitted to the emergency department. Values are numbers (percentages) unless stated otherwise

Characteristics	All patients (n=7607)	Low risk (n=1242)	Medium risk (n=5484)	High risk (n=881)
Demographics				
Mean (SD) age, years	68.5 (14.7)	65.3 (14.5)	68.1 (14.8)	75 (11.7)
Median (interquartile range) age, years	70 (58-80)	66 (54-77)	69 (58-80)	76 (68-84)
Age range, years	18-103	18-98	18-103	36-99
Female sex	3982 (52.3)	695 (56.0)	2936 (53.5)	351 (39.8)
Clinical features: history				
Arrival by ambulance	2765/7605 (36.4)	365/1242 (29.4)	1962/5482 (35.8)	438/881 (49.7)
First ever TIA	5706/7589 (75.2)	765/1237 (61.8)	4208/5474 (76.9)	733/878 (83.5)
Duration of symptoms:	(n=7543)	(n=1222)	(n=5445)	(n=876)
<1 minute	221 (2.9)	132 (10.8)	86 (1.6)	3 (0.3)
1-4 minutes	468 (6.2)	232 (19.0)	226 (4.2)	10 (1.1)
5-9 minutes	486 (6.4)	216 (17.7)	247 (4.5)	23 (2.6)
10-29 minutes	1383 (18.3)	130 (10.6)	1076 (19.8)	177 (20.2)
30-59 minutes	1120 (14.8)	126 (10.3)	844 (15.5)	150 (17.1)
≥60 minutes	3865 (51.2)	386 (31.6)	2966 (54.5)	513 (58.6)
History of altered sensation	3269/7521 (43.5)	470/1231 (38.2)	2465/5419 (45.5)	334/871 (38.3)
History of weakness	3019/7544 (40.0)	273/1234 (22.1)	2164/5435 (39.8)	582/875 (66.5)
Language disturbance	2943/7442 (39.5)	327/1208 (27.1)	2109/5370 (39.3)	507/864 (58.7)
Light-headedness	1297/7281 (17.8)	302/1201 (25.1)	871/5246 (16.6)	124/834 (14.9)
Vertigo	779/7338 (10.6)	474/1222 (38.8)	281/5278 (5.3)	24/838 (2.9)
Gait disturbance	1571/7356 (21.4)	226/1203 (18.8)	1027/5311 (19.3)	318/842 (37.8)
Visual loss	1069/7113 (15.0)	254/1158 (21.9)	740/5139 (14.4)	75/816 (9.2)
Clinical features: examination				
Mean (SD) initial systolic blood pressure, mm Hg (n=7597)	151.9 (26.1)	150.6 (24.1)	151.7 (25.7)	155.4 (30.4)
Mean (SD) initial diastolic blood pressure, mm Hg (n=7594)	82.9 (13.7)	82.9 (11.8)	82.7 (13.3)	84.3 (18.3)
Mean (SD) initial heart rate, bpm (n=7600)	77.6 (15.0)	77.2 (14.2)	77.7 (14.9)	77.6 (16.3)
Weakness	997/7547 (13.2)	57/1234 (4.6)	720/5440 (13.2)	220/873 (25.2)
Altered sensation	868/7489 (11.6)	105/1229 (8.5)	675/5395 (12.5)	88/865 (10.2)
Any speech difficulty	850/7523 (11.3)	51/1226 (4.2)	617/5421 (11.4)	182/873 (20.8)
Gait abnormality	617/7397 (8.3)	105/1222 (8.6)	383/5338 (7.2)	129/837 (15.4)
Dysarthria	564/7486 (7.5)	30/1229 (2.4)	397/5392 (7.4)	137/868 (15.8)
Pronator drift	405/7053 (5.7)	33/1157 (2.9)	278/5095 (5.5)	94/801 (11.7)
Aphasia	268/7486 (3.6)	18/1226 (1.5)	205/5392 (3.8)	45/868 (5.2)
Abnormal finger-nose test	262/7312 (3.6)	30/1213 (2.5)	182/5268 (3.5)	50/831 (6.0)
Clinical features: past medical history	**(n=7592)**	**(n=1238)**	**(n=5474)**	**(n=880)**
Hypertension	4505 (59.3)	599 (48.4)	3191 (58.3)	715 (81.3)
High cholesterol	2772 (36.5)	379 (30.6)	1973 (36.0)	420 (47.7)
Diabetes mellitus	1448 (19.1)	138 (11.1)	,002 (18.3)	308 (35.0)
Coronary artery disease	1289 (17.0)	101 (8.2)	866 (15.8)	322 (36.6)
Known previous stroke	976 (12.9)	119 (9.6)	672 (12.3)	185 (21.0)
Current smoker	840 (11.1)	128 (10.3)	616 (11.3)	96 (10.9)
Atrial fibrillation	806 (10.6)	96 (7.8)	535 (9.8)	175 (19.9)
Peripheral vascular disease	269 (3.5)	17 (1.4)	176 (3.2)	76 (8.6)
Carotid stenosis	251 (3.3)	9 (0.7)	138 (2.5)	104 (11.8)
Diagnostic tests in emergency department				
Computed tomography of head	7337 (96.5)	1191 (95.9)	5287 (96.4)	859 (97.5)
Evidence of acute or old infarction	2080 (27.3)	172 (13.8)	1413 (25.8)	495 (56.2)
Electrocardiography	6923 (91.0)	1114 (89.7)	4993 (91.0)	816 (92.6)
Evidence of atrial fibrillation	425 (5.6)	22 (1.8)	255 (4.7)	148 (16.8)
Magnetic resonance imaging of head	323 (4.2)	37 (3.0)	244 (4.4)	42 (4.8)
Carotid Doppler	4382 (57.6)	684 (55.1)	3225 (58.8)	473 (53.7)
Computed tomography angiography of neck	2085 (27.4)	309 (24.9)	1493 (27.2)	283 (32.1)
Routine drugs at time of index TIA				
Antihypertensive	3579 (47.0)	461 (37.1)	2522 (46.0)	596 (67.7)
Any antithrombotic	3274 (43.0)	231 (18.6)	2328 (42.5)	715 (81.2)
Aspirin	2274 (29.9)	101 (8.1)	1593 (29.0)	580 (65.8)
Clopidogrel	588 (7.7)	31 (2.5)	423 (7.7)	134 (15.2)
Warfarin	348 (4.6)	66 (5.3)	224 (4.1)	58 (6.6)
Dipyridamole/aspirin	55 (0.7)	3 (0.2)	41 (0.7)	11 (1.2)
Ticlopidine	6 (0.1)	2 (0.2)	3 (0.1)	1 (0.1)
Other anticoagulant	367 (4.8)	49 (3.9)	269 (4.9)	49 (5.6)
Statin	2772 (36.4)	342 (27.5)	1946 (35.5)	484 (54.9)

Table 2 | Continued

Characteristics	All patients (n=7607)	Low risk (n=1242)	Medium risk (n=5484)	High risk (n=881)
Drugs on discharge				
Antihypertensive	3728 (49.0)	473 (38.1)	2634 (48.0)	621 (70.5)
Any antithrombotic	6667 (87.6)	1002 (80.7)	4807 (87.7)	858 (97.4)
Aspirin	5477 (72.0)	866 (69.7)	3943 (71.9)	668 (75.8)
Clopidogrel	1251 (16.4)	65 (5.2)	898 (16.4)	288 (32.7)
Warfarin	362 (4.8)	66 (5.3)	233 (4.2)	63 (7.2)
Dipyridamole/aspirin	136 (1.8)	8 (0.6)	97 (1.8)	31 (3.5)
Ticlopidine	6 (0.1)	2 (0.2)	3 (0.1)	1 (0.1)
Other anticoagulant	413 (5.4)	51 (4.1)	296 (5.4)	66 (7.5)
Statin	3109 (40.9)	401 (32.3)	2195 (40.0)	513 (58.2)
Primary outcome				
Stroke or carotid revascularisation ≤7 days	183 (2.4)	6 (0.5)	124 (2.3)	53 (6.0)
Secondary outcomes				
Carotid revascularisation ≤7 days from index visit	84 (1.1)	3 (0.2)	52 (0.9)	29 (3.3)
Carotid revascularisation ≤90 days from index visit	156 (2.1)	12 (1.0)	95 (1.7)	49 (5.6)
Carotid endarterectomy ≤7 days from index visit	69 (0.9)	3 (0.2)	42 (0.8)	24 (2.7)
Carotid endarterectomy ≤90 days from index visit	130 (1.7)	12 (1.0)	80 (1.5)	38 (4.3)
Carotid stent ≤7 days from index visit	16 (0.2)	0 (0)	11 (0.2)	5 (0.6)
Carotid stent ≤90 days from index visit	29 (0.4)	0 (0)	17 (0.3)	12 (1.4)
Cumulative stroke ≤2 days from index visit	70 (0.9)	1 (0.1)	51 (0.9)	18 (2.0)
Cumulative stroke ≤7 days from index visit	108 (1.4)	3 (0.2)	81 (1.5)	24 (2.7)
Cumulative stroke ≤30 days from index visit	153 (2.0)	4 (0.3)	116 (2.1)	33 (3.7)
Cumulative stroke ≤90 days from index visit	192 (2.5)	5 (0.4)	141 (2.6)	46 (5.2)
Cumulative recurrent TIA ≤2 days from index visit	81 (1.1)	5 (0.4)	56 (1.0)	20 (2.3)
Cumulative recurrent TIA ≤7 days from index visit	154 (2.0)	15 (1.2)	108 (2.0)	31 (3.5)
Cumulative recurrent TIA ≤30 days from index visit	261 (3.4)	30 (2.4)	180 (3.3)	51 (5.8)
Cumulative recurrent TIA ≤90 days from index visit	357 (4.7)	44 (3.5)	244 (4.4)	69 (7.8)
Myocardial infarction ≤90 days from index visit	26 (0.3)	2 (0.2)	16 (0.3)	8 (0.9)
Admitted to hospital during index visit	441 (5.8)	40 (3.2)	298 (5.4)	103 (11.7)

one in eight at high risk (>5% risk; interval likelihood ratio 2.56, 2.02 to 3.25). The remainder were at medium risk, with a subsequent seven day event rate of 2.3% and an interval likelihood ratio of 0.94 (0.85 to 1.04). These risk strata were similar for the secondary outcome of subsequent stroke (table 4) and for risk stratification at both two and 90 days (appendix 2).

Neither the ABCD2 nor the ABCD2i score was able to classify any patients as being low risk (<1% for subsequent stroke or carotid revascularisation within seven days). Moreover, these rules classified all but 3-7% of patients into a single, medium risk stratum (appendix 3 and appendix 4). The area under the curve for the Canadian TIA Score was higher than that of the ABCD2 or ABCD2i score (0.70 (95% confidence interval 0.66 to 0.73) versus 0.60 (0.55 to 0.64) or 0.64 (0.59 to 0.68)), indicating improved classification. The DeLong comparison of the C statistics for stroke or carotid revascularisation within seven days found a difference in the C statistic of 0.10 (95% confidence

Table 3 | Classification performance, sensitivity, and specificity by score and risk category of Canadian TIA Score for subsequent stroke or carotid revascularisation within 7 days of index emergency department visit for transient ischaemic attack (n=7607)

Score	No (%) total patients	No (%) estimated stroke or carotid revascularisation ≤7 days	No (%) observed stroke or carotid revascularization ≤7 days	Risk category	Proportion of patients (%)	Sensitivity (95% CI)	Specificity (95% CI)
−3	4 (0.1)	0 (0.2)	0 (0)			1.00 (0.98 to 1.00)	0.00 (0.00 to 0.00)
−2	2 (0.0)	0 (0.2)	0 (0)			1.00 (0.98 to 1.00)	0.00 (0.00 to 0.00)
−1	35 (0.5)	0 (0.3)	0 (0)			1.00 (0.98 to 1.00)	0.00 (0.00 to 0.00)
0	80 (1.1)	0 (0.4)	0 (0)	Low	16.3	1.00 (0.98 to 1.00)	0.01 (0.00 to 0.01)
1	148 (1.9)	1 (0.5)	1 (0.7)			1.00 (0.98 to 1.00)	0.02 (0.01 to 0.02)
2	432 (5.7)	3 (0.7)	3 (0.7)			0.99 (0.97 to 1.00)	0.04 (0.03 to 0.04)
3	541 (7.1)	5 (0.9)	2 (0.4)			0.98 (0.94 to 0.99)	0.09 (0.09 to 0.10)
4	1245 (16.4)	15 (1.2)	15 (1.2)			0.97 (0.93 to 0.99)	0.17 (0.16 to 0.18)
5	1499 (19.7)	24 (1.6)	22 (1.5)			0.88 (0.83 to 0.93)	0.33 (0.32 to 0.34)
6	1042 (13.7)	23 (2.2)	28 (2.7)	Medium	72.1	0.76 (0.70 to 0.82)	0.53 (0.52 to 0.54)
7	920 (12.1)	26 (2.8)	25 (2.7)			0.61 (0.54 to 0.68)	0.67 (0.66 to 0.68)
8	778 (10.2)	29 (3.7)	34 (4.4)			0.47 (0.40 to 0.55)	0.79 (0.78 to 0.80)
9	467 (6.1)	23 (4.9)	27 (5.8)			0.29 (0.22 to 0.36)	0.89 (0.88 to 0.90)
10	228 (3.0)	15 (6.4)	11 (4.8)			0.14 (0.09 to 0.20)	0.95 (0.94 to 0.95)
11	117 (1.5)	10 (8.3)	10 (8.5)			0.08 (0.04 to 0.13)	0.98 (0.97 to 0.98)
12	54 (0.7)	6 (10.7)	2 (3.7)	High	11.6	0.02 (0.01 to 0.06)	0.99 (0.99 to 0.99)
13	13 (0.2)	2 (13.7)	1 (7.7)			0.01 (0.00 to 0.04)	1.00 (1.00 to 1.00)
14	2 (0.0)	0 (17.4)	1 (50.0)			0.01 (0.00 to 0.03)	1.00 (1.00 to 1.00)

Table 4 | Canadian TIA Score: interval likelihood ratios and risk of outcome within 7 days (n=7607)

	Outcome				
	Yes	No	Interval likelihood ratio (95%CI)	Observed risk (%)	Estimated risk (%)
Subsequent stroke/carotid revascularisation					
Low risk (−3 to 3)	6	1236	0.20 (0.09 to 0.44)	0.5	0.7
Medium risk (4 to 8)	124	5360	0.94 (0.85 to 1.04)	2.3	2.1
High risk (≥9)	52	829	2.56 (2.02 to 3.25)	5.9	6.3
Subsequent stroke					
Low risk (−3 to 3)	3	1239	0.17 (0.06 to 0.51)	0.2	0.5
Medium risk (4 to 8)	81	5403	1.04 (0.93 to 1.16)	1.5	1.3
High risk (≥9)	24	857	1.94 (1.36 to 2.78)	2.7	3.3

interval 0.05 to 0.15; P<0.001) between the Canadian TIA Score and the ABCD2 score and a difference in the C statistic of 0.06 (0.01 to 0.11; P=0.01) for the Canadian TIA Score versus the ABCD2i score (table 5 and fig 1). The ABCD2i score, but not the ABCD2 score, classified nearly half of patients as being at low risk for the secondary outcome restricted to subsequent stroke only, including about one third (25/74) of the patients who had carotid revascularisation but remained stroke-free at seven days, to this risk stratum.

Figure 2 shows that the absolute net reclassification index between the Canadian TIA Score and the ABCD2 score for stroke or carotid revascularisation within seven days was 12.0%. The absolute net reclassification index between the Canadian TIA Score and the ABCD2i score was 8.5%.

Discussion

Our study validates the predictive performance of the Canadian TIA Score in a broad sample of patients prospectively enrolled in the emergency department with a diagnosis of transient ischaemic attack or minor stroke. To improve the generalisability of the score, we included both community and academic centres, including six new sites that were not involved in the derivation study. The score was able to correctly stratify many more patients into pre-specified risk zones than were other scores based on the ABCD paradigm. Having withstood prospective validation in a newly assembled, contemporaneous cohort, and satisfying stringent criteria for the development of a clinical decision rule/score, this tool can now be adopted into clinical practice.

The performance of the score was consistent irrespective of whether we included immediate carotid revascularisation (that is, a potentially averted early stroke) as an outcome of interest. The ability of the score to stratify patients according to risk remained robust when we used only the outcome of subsequent stroke. Among the various changes in the management of transient ischaemic attack in the decade since we began developing this decision tool, carotid revascularisation for patients with high grades of carotid disease has been among the most notable, and its widespread adoption in Canadian stroke centres necessitated a change to the original study outcome of interest. We also increased our target sample size by half to ensure that we had sufficient precision for the original outcome of subsequent stroke alone, without considering carotid revascularisation.

The Canadian TIA Score performed significantly better than the ABCD2 scores. The ABCD2 based scores classified almost all patients as being at medium risk when using our pre-specified risk thresholds (low risk <1%, medium risk 1-5%, high risk >5%). This resulted in more patients with subsequent events being classified as at high risk by the Canadian TIA Score than by either of the ABCD2 scores. It also resulted in more patients without subsequent events being classified as at low risk. However, more patients were deemed to be at high risk by the Canadian TIA Score than both the ABCD2 scores (using thresholds of 6 for ABCD2 and 9 for ABCD2i). Both the ABCD2 and ABCD2i were designed as dichotomous scores. Therefore, in practice, many of the patients at medium risk would be deemed to be at high risk by the respective ABCD2 score. This dichotomy is limiting for practising physicians, and we believe that having three levels of risk provides clinicians with more options for management. When we compared the two ABCD2 scores, the ABCD2i score was better than the ABCD2 score; it identified many patients at low risk for the secondary outcome of subsequent stroke, but at the expense of missing many patients who underwent early carotid revascularisation. Although our score is more complex and is not intended to be memorised, it requires only routinely available information from the history, bedside assessment, and test results to stratify patients. It can be readily used and applied by

Table 5 | DeLong method for comparing Canadian TIA Score with ABCD2 and ABCD2i scores for subsequent stroke or carotid revascularisation within 7 days (n=7607)

Score or comparison	AUC (95% CI)	Difference in AUC (95% CI)	P value
Canadian TIA Score	0.70 (0.66 to 0.73)	-	-
ABCD2	0.60 (0.56 to 0.64)	-	-
ABCD2i	0.64 (0.59 to 0.68)	-	-
Canadian TIA Score *v* ABCD2	-	0.10 (0.05 to 0.15)	<0.001
Canadian TIA Score *v* ABCD2i	-	0.06 (0.01 to 0.11)	0.01

AUC=area under curve; TIA=transient ischaemic attack.

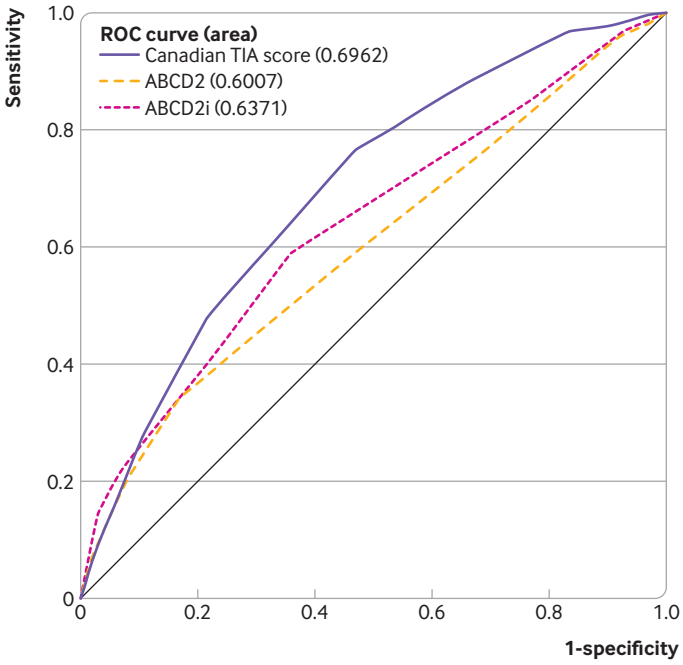

Fig 1 | Receiver operating characteristic (ROC) curve for comparison of Canadian TIA Score with ABCD2 and ABCD2i scores for subsequent stroke or carotid revascularisation within 7 days (n=7607)

physicians in the emergency department, as it does not require advanced neuroimaging, which is often unavailable. It allows one to customise the urgency of, for example, advanced neuroimaging or to inform the decision surrounding inpatient admission versus outpatient specialty consultation according to local preferences or to incorporate patients' preferences. Many hospitals are unable to offer 24/7 access to magnetic resonance imaging and/or need to transfer patients for specialty consultation. Stratifying the risk for patients allows for more standardised care, more equitable deployment of constrained resources, and probably better outcomes.[29 30]

Comparisons with other studies

The definition of transient ischaemic attack continues to evolve and requires absence of infarction on magnetic resonance imaging.[31] Although this definition provides greater diagnostic accuracy and excludes many non-ischaemic aetiologies that mimic transient ischaemic attack or stroke than the World Health Organization's time based definition, it is not practical in emergency departments in much of the US, most of Canada, and most of the world, given the requirement for immediate magnetic resonance imaging. Hence, our work has emphasised a working emergency department diagnosis of transient ischaemic attack or minor stroke as the target population for the Canadian TIA Score.[9] Conversely, an abnormal magnetic resonance imaging scan alone confers only a modest increase in subsequent risk of stroke, as shown in a recent study of patients diagnosed as having a possible transient ischaemic attack or minor stroke: very few had a subsequent stroke at one year despite 13.5% having abnormalities on imaging. Patients high risk features with or without positive diffusion weighted magnetic resonance imaging scans had a combined subsequent stroke rate of 0.7%.[32] Five high risk features were identified for the composite outcome of subsequent stroke, subsequent transient ischaemic attack, death, or myocardial infarction, but the authors concluded that they were not sensitive enough in identifying patients with subsequent events to be used clinically.

We had previously surveyed both neurologists and emergency physicians to identify thresholds of stroke risk that would alter clinical decisions.[26 27] In these studies, respondents indicated that patients with a subsequent risk of stroke below 1% were most appropriate for outpatient investigation, whereas patients with a subsequent risk of stroke above 5% constitute a high risk group that might benefit from comprehensive investigation, more intensive therapy, and possible admission at the time of the initial emergency department visit. These opinions reflect contemporary thinking in Canada but can serve as a starting point for important discussions on the allocation of resources in other settings, as well as for planning a future implementation study.

Strengths and limitations of study

Our study included a new cohort of patients (temporal validation) from new study sites (geographical validation) and included both academic and community hospitals. This large multicentre cohort study of patients with transient ischaemic attack prospectively assessed findings from the history, examination, and investigations to identify patients at highest risk for an impending stroke. We followed the methodological standards recommended for validation studies.[13-15] Our study enrolled patients diagnosed, mostly by front line emergency physicians, as having had a transient ischaemic attack or minor stroke. Although some patients with mimics of transient ischaemic attack (that is, neurological symptoms not due to a transient ischaemic attack or stroke) were necessarily enrolled, these very patients are nevertheless part of the intended target population for risk stratification in the emergency department and comparable settings. Our use of blinded adjudication committees to assess subsequent strokes provided rigorous outcome classification. These committees were blinded to the initial emergency department visit documentation but used all sources of subsequent information available (telephone follow-up, clinic visits, testing, admissions). Our study also compared, prospectively, the ABCD2 and ABCD2i scores.

The use of a composite outcome could be criticised, given that a subsequent stroke typically has greater morbidity than a procedure to revascularise a carotid artery. However, we fully validated the score using the original outcome restricted to subsequent stroke (n=108). Some potentially eligible patients were missed, but we enrolled more than 80% of eligible patients, and missed patients seemed to be similar to enrolled patients. In addition, a small number of

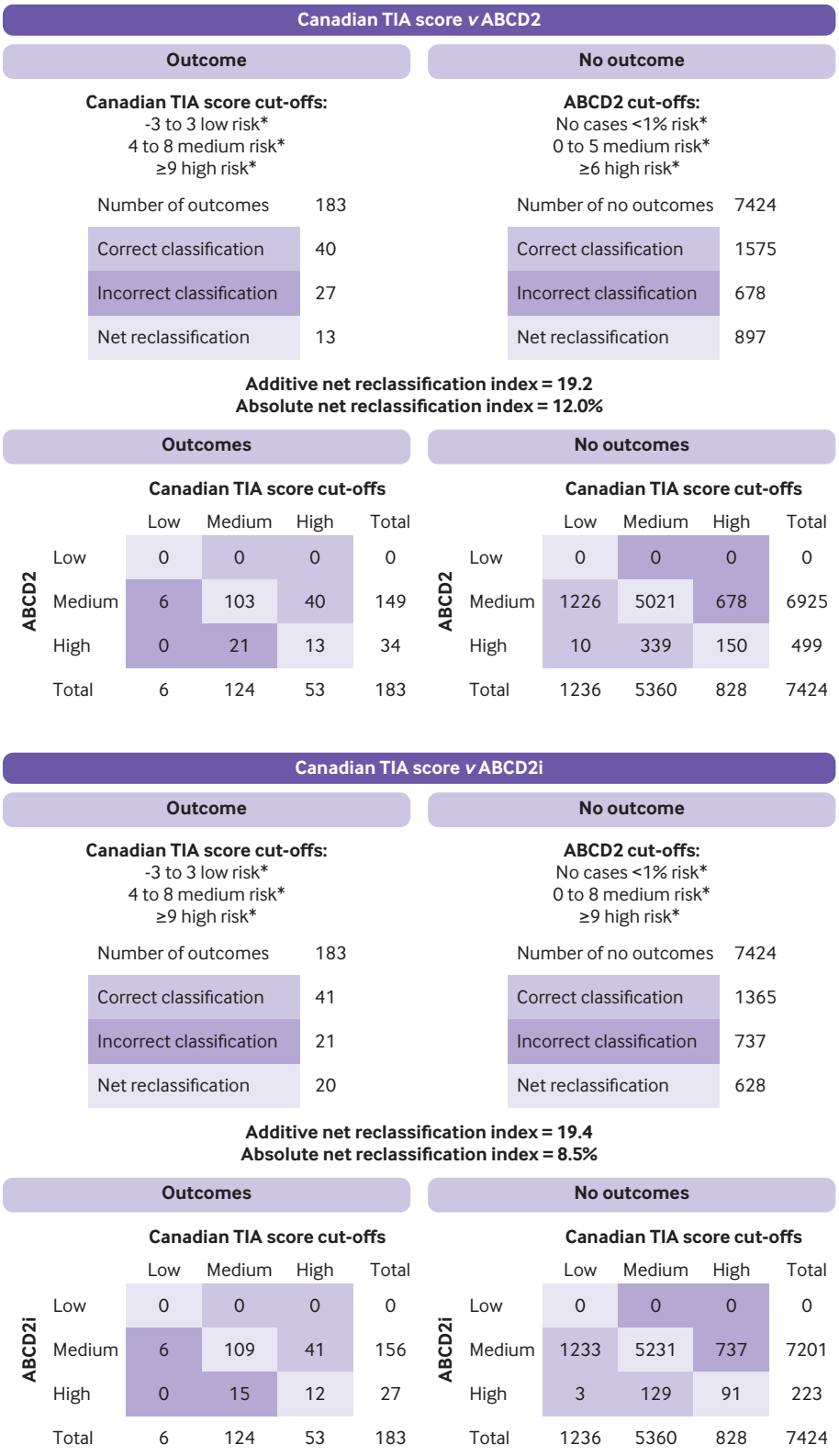

Fig 2 | Net reclassification index comparing Canadian TIA Score with ABCD2 and ABCD2i for subsequent stroke or carotid revascularisation within 7 days (n=7607). *Low risk defined by risk of outcome of ‹1%, medium risk 1-5%, and high risk ›5%

patients were lost to follow-up. Given that the rate of loss to follow-up was less than 1%, these cases are not likely to have a significant effect on our results.

The Canadian TIA Score includes 13 variables, so clinicians will probably need to use an online calculator or smartphone application to calculate the risk of their

patients. Given that physicians already use these tools for many patients, this is likely a minor limitation and represents the heterogeneity of risk assessment for cerebral ischaemia.

Policy implications

Clinicians may now use the Canadian TIA Score to stratify patients as being at low, medium, or high risk for subsequent early stroke (with or without early carotid revascularisation). The optimal management pathway at the local or regional level can be determined on the basis of the expected risk at a given risk category (for example, same day computed tomography with routine follow-up for patients at low risk, computed tomography angiography and rapid follow-up for those at medium risk, and neurology consultation in the emergency department for those at high risk).

Research implications

A prospective multicentre implementation study following the established guidelines to implement a clinical prediction score is now needed to assess the impact of the Canadian TIA Score when applied in clinical practice. Additional research can further identify specific cut-off points for any given intervention and inform efforts to optimise stroke prevention. Further refinements and simplification of the rule are also important, especially as changes in diagnostic specificity and the intensity of initial investigation and treatment of transient ischaemic attack continue to evolve.

Conclusion

The Canadian TIA Score identifies the risk of patients with transient ischaemic attack for subsequent stroke or carotid artery revascularisation within seven days. Incorporating this validated risk estimate into management plans should improve decisions on the benefits of hospital admission at the index visit, urgency of testing and interventions, and prioritisation of specialist follow-up for patients discharged from the emergency department.

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Ethical approval: The study was approved by the research ethics board at each site as meeting the requirements for a waiver of written informed consent. Verbal consent was obtained at the time of each telephone call for patients contacted for follow-up.

Data sharing: Requests for sharing of the data will be considered and reviewed by the study's steering committee. Requests can be made to the corresponding author.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: There is no formal plan to disseminate these results to study participants. All study sites have received study results. The results of this work will be disseminated through social media, conferences, and creation of an infographic. The results will be incorporated in the Ottawa Rules App, which will assist clinicians using the score.

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Web appendix: Supplementary appendices