ABCD2 score and secondary stroke prevention

Meta-analysis and effect per 1,000 patients triaged

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ABSTRACT

Objective: Patients with TIA have high risk of recurrent stroke and require rapid assessment and treatment. The ABCD2 clinical risk prediction score is recommended for patient triage by stroke risk, but its ability to stratify by known risk factors and effect on clinic workload are unknown.

Methods: We performed a systematic review and meta-analysis of all studies published between January 2005 and September 2014 that reported proportions of true TIA/minor stroke or mimics, risk factors, and recurrent stroke rates, dichotomized to ABCD2 score </≥4. We calculated the effect per 1,000 patients triaged on stroke prevention services.

Results: Twenty-nine studies, 13,766 TIA patients (range 69–1,679), were relevant: 48% calculated the ABCD2 score retrospectively; few reported on the ABCD2 score's ability to identify TIA mimics or use by nonspecialists. Meta-analysis showed that ABCD2 ≥4 was sensitive (86.7%, 95% confidence interval [CI] 81.4%–90.7%) but not specific (35.4%, 95% CI 33.3%–37.6%) for recurrent stroke within 7 days. Additionally, 20% of patients with ABCD2 <4 had >50% carotid stenosis or atrial fibrillation (AF); 35%–41% of TIA mimics, and 66% of true TIAs, had ABCD2 score ≥4. Among 1,000 patients attending stroke prevention services, including the 45% with mimics, 52% of patients would have an ABCD2 score ≥4.

Conclusion: The ABCD2 score does not reliably discriminate those at low and high risk of early recurrent stroke, identify patients with carotid stenosis or AF needing urgent intervention, or streamline clinic workload. Stroke prevention services need adequate capacity for prompt specialist clinical assessment of all suspected TIA patients for correct patient management.
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GLOSSARY

AF = atrial fibrillation; **CI** = confidence interval; **OR** = odds ratio; **ROC** = receiver operator characteristic.

The estimated incidence of TIA ranges from 200,000 to 500,000 in the United States.[1] Stroke risk is highest, and secondary prevention most effective, early after TIA.[2] The ABCD and ABCD2 scores were developed as clinical decision rules for assessing, in nonspecialist settings, the risk of stroke in a patient with suspected TIA, so as to fast-track those at high risk for urgent treatment.[3] The ABCD2 score allocates points for key clinical and vascular risk variables and has achieved particular prominence among several clinical risk prediction scores.[4] Many stroke prevention guidelines[5,6] recommend specialist assessment and investigation within 24 hours of TIA/minor stroke for patients with high ABCD2 score (≥4) and within 1 week for patients with low scores (<4), these cutpoints being chosen based on performance on receiver operator characteristic (ROC) curves (area under the curve 0.72).[7] Use of the ABDC2 score in some countries[5] is incentivized through extra payments.[8] However, the ABCD2 score may have limitations for identifying important categories of patients, e.g., those with tight carotid stenosis or atrial fibrillation (AF),[9,10] and may not perform as well in the field as suggested in early reports and guidelines.[11,12]

In view of these doubts, we assessed all available data to determine the extent to which the ABCD2 score had been tested in stroke prevention in circumstances in which guidelines[5,6]

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now promote its use, and its ability to predict stroke recurrence in patients at high (≥4) and low (<4) risk of stroke; differentiate patients with mimics from true stroke/TIA; identify carotid stenosis or AF; and estimate its effect on proportions of patients entering fast- or slow-track assessment in a typical stroke prevention service per 1,000 patients assessed.

METHODS We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] We aimed to identify all published studies in which the ABCD2 score was used to predict risk of stroke among patients with suspected TIA or minor stroke, irrespective of the clinical setting or study design, that dichotomized the ABCD2 score at </≥4, and that reported on the actual recurrent stroke rate.

Identification of studies. We searched indexed records in MEDLINE (Ovid) and EMBASE from January 2005 to September 2014 to reflect the development and introduction of the ABCD2 prediction score into clinical practice, including in an era before the proposed tissue-based definition of stroke and TIA[14] was in widespread use. The MEDLINE search strategy included both subject headings (MeSH terms) and text words for the target condition (e.g., stroke, TIA, minor stroke) and prediction score. We translated the MEDLINE MeSH terms into the corresponding terms in the Emtree vocabulary for EMBASE. For full search strategies, see appendix e-1 on the *Neurology*® Web site at Neurology.org. We hand-searched stroke conference proceedings, contacted experts in the field, and perused reference lists to identify further published studies for possible inclusion.

Inclusion/exclusion criteria. One review author (M.B.) examined the identified titles and abstracts and retrieved all potentially relevant citations. We retained full-text articles if they studied the application of the ABCD2 score in cohorts of suspected TIA and minor stroke patients and reported early risk of stroke at 7 days, 90 days, or beyond 90 days. We excluded studies that did not consider the incidence of further stroke in TIA/minor stroke patients, did not assess patients by means of the ABCD2 score, did not use the cutoff score of 4, only reported on ABCD2 with imaging variables, did not report original data, or were only reported in conference abstracts. We applied no language restrictions.

Quality assessment, data extraction. Two review authors (M.B., H.M.) independently extracted summary data and assessed study methodologic quality (an individual subject meta-analysis was beyond the scope of available resources). We resolved disagreements by discussion with a third author (J.M.W.). We recorded study methods (e.g., clinical setting, design), patient characteristics (first vs recurrent TIA; cardiac or carotid stenosis risk factors), and outcomes (recurrent stroke at 7, 90, and beyond 90 days). We used the definition of tight carotid stenosis as stated in each article but generally considered carotid stenosis of >50% by North American Symptomatic Carotid Endarterectomy Trial to be tight. We did not use a specific appraisal tool to assess study quality as, at present, there is no valid, recommended instrument for assessing nonrandomized evidence. Nevertheless, we identified the most relevant methodologic characteristics that were most likely to introduce potential biases: prospective vs retrospective design, data source for cohort identification (e.g., registries, databases, case notes), patient selection criteria, spectrum of disease severity, definition of TIA, timing of clinical assessment, specialty of evaluating clinicians, and method of outcome ascertainment (prospective assessment vs retrospective case note review). These characteristics are clearly reported in the results tables.

Data synthesis. For each study, we calculated the total number of patients with ABCD2 score </≥4 and the proportion of patients in each ABCD2 dichotomized category with recurrent stroke at 7, 90, or >90 days. We calculated the pooled risks of stroke for ABCD2 score </≥4 at 7, 90, and >90 days by univariate random effects meta-analyses with within-study variance modeled as binomial. We evaluated the proportion of recurrent stroke patients at 7, 90, or >90 days with ABCD2 score </≥4 by bivariate ROC curve random effects meta-analyses. We first analyzed all studies that reported recurrent stroke at 7, 90, or >90 days; second, we analyzed just those studies that reported recurrent stroke at both 7 and 90 days to reduce the impact of methodologic differences between studies. We calculated estimates of sensitivity, specificity, and positive and negative predictive values of the ABCD2 score for a hypothetical cohort of 1,000 suspected TIA patients (+/− mimics), expressed as the proportion with recurrent stroke per 1,000 patients assessed, to improve the clinical relevance of the results. All analyses were performed in R 2.14.2 (cran.r-project.org/).

Role of the funding source. The study funder had no role in the study design, collection, analysis, or interpretation of data, writing, or in the decision to submit the paper for publication.

RESULTS **Included/excluded studies.** Electronic searches identified 6,406 citations; 111 were potentially relevant. Hand-searching reference lists and recent issues of *Stroke* found 2 further reports. We excluded 84 articles, the commonest reason being insufficient data to calculate ABCD2 score </≥4 (figure e-1), leaving 29 studies published in 31 reports, including 15 prospective and 14 retrospective observational cohort studies, ranging in size from 69 to 1,679 patients (total 13,766 TIA/minor stroke patients).

Characteristics of included studies. The included studies varied in terms of their methodologic quality (table e-1). All studies used a time-based definition of TIA (3 did not report the definition[15–17]).[18] Five studies assessed population-based cohorts,[19–22] 4 studied hospital-based cohorts,[16,23–25] 10 studied patients from emergency departments,[15,26–34] and 10 studied patients from specialist stroke or neurology units.[3,9,35–42] Timing of patient assessment after TIA varied: within 24 hours of symptom onset (7 studies), within 48 hours (4 studies), within 7 days (4 studies), "as soon as possible after the event" but did not give a time (3 studies), at median 15 days (1 study), or did not provide this information (9 studies).

The ABCD2 score was derived directly from patient assessment in 16 studies; the remaining 13 studies calculated the ABCD2 score retrospectively from medical notes. All except 3 studies[29,43,44] included only patients with a definite or confirmed TIA by a neurologist/stroke physician and excluded TIA mimics. TIA diagnosis was made by a

neurologist in 15 studies; by an emergency medicine physician in 7 studies; initially by an emergency medicine physician and subsequently confirmed by a neurologist in 2 studies; by a stroke physician in another 2 studies; and was not reported in the remaining 3 studies. Only 5 studies stated that 45%–50% of TIA patients received antithrombotic therapy[15,26,28,32,42]; one study reported that 15% of patients received aspirin.[30]

Ascertainment of stroke events after TIA was performed by face-to-face or telephone assessment in 18 studies, by medical record review alone in 7, or with some telephone interviews in 3 studies, and was not clearly reported in one study (table e-1).

Main findings: Stroke recurrence rates by ABCD2 score </≥4. Seventeen of 29 studies (7,072 patients) reported stroke events at 7 days,[3,17,19–23,26–28,30,31,35,36,38,41,42] 22/29 studies (11,029 patients) reported stroke at 90 days,[3,9,15,17,22,25,26,28–35,37–39,41,42] and 4/29 studies (1,862 patients) reported stroke events at >90 days (table 1).[16,24,34,40] The proportions of patients in ABCD2 score categories </≥4 was very consistent for each time point—about two thirds of patients were classed as ABCD2 ≥4 and one third as <4. A larger proportion of patients with ABCD2 score ≥4 had recurrent stroke at all 3 time points than those with ABCD2 score <4 (table 1, figure e-2, A–C): e.g., 7.2% (95% confidence interval [CI] 4.8%–10.8%) of patients with ABCD2 score ≥4 had recurrent stroke by 7 days compared with 2.4% (95% CI 1.1%–5.4%) of patients with ABCD2 <4. There was considerable between-study heterogeneity and wide CIs, possibly reflecting variation in study methods or different patient populations rather than true differences in stroke rates at 7 and 90 days.

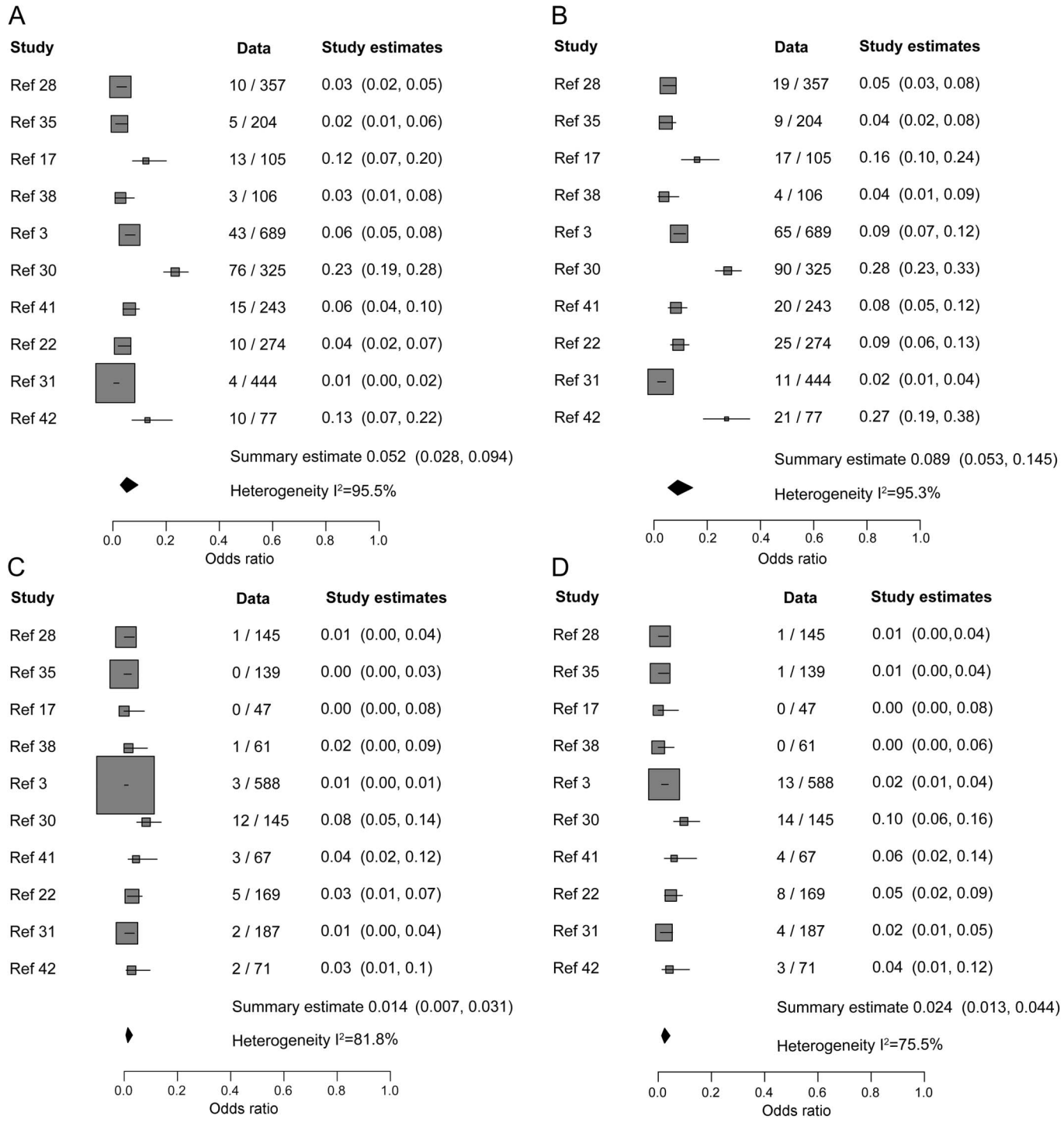
To reduce the potential impact of study methods on heterogeneity, we analyzed the 10 studies (4,443 patients) that provided data on stroke recurrence at both 7 and 90 days.[3,17,22,28,30,31,35,38,41,42] One other study apparently reporting on stroke recurrence at both 7 and 90 days (published in 2 reports[26,45]) was excluded as the 90-day stroke recurrence was low compared to that at 7 days (table e-2). None of these 10 studies provided data on stroke risk >90 days; 5/10 studies (2,019/4,443 patients, 45%) identified patients retrospectively. In these 10 studies, about a third of patients had an ABCD2 score <4 and two thirds had a score of ≥4. The pooled proportion with recurrent stroke was lower, with narrower CIs, than for all studies: at 7 days, 5.2% (95% CI 2.8–9.4%) of patients with ABCD2 score ≥4 and 1.4% (95% CI 0.7–3.1%) of patients with ABCD2 <4 had recurrent stroke; at 90 days, 8.9% (95% CI 5.3–14.5%) of patients with ABCD2 score ≥4 and 2.4% (95% CI 1.3–4.4%) of patients with ABCD2 <4 had recurrent stroke. Forest plots (figure 1) show reduced heterogeneity compared with data from all studies (figure e-2, A–C). The sensitivity of the ABCD2 score ≥4 to predict stroke was 86.7 (95% CI 81.4–90.7) at 7 days and 85.4 (95% CI 81.1–88.9) at 90 days; specificity was 35.4 (95% CI 33.3–38.3) at 7 days and 36.2 (95% CI 34.0–37.6) at 90 days in these 10 studies.

ABCD2 and specific risk factors. Four studies provided data on recurrent stroke by ABCD2 score and carotid stenosis, AF, or both, totaling 2,579 patients.[21,22,46,47] Of 1,132 patients with ABCD2 score <4, 14.8% had carotid stenosis >50% compared with 15.4% of

Table 1 Proportions with ABCD2 score ≥/<4, number of recurrent strokes, and raw and pooled percentage stroke risks at 7, 90, and >90 days for all included studies and just the 9 studies that reported at both 7 and 90 days

	ABCD2 score	n/N (%)	N recurrent strokes, raw (%)	Pooled %	95% CI
At 7 days					
All studies (17/29)[3,17,19-23,26-28,30,31,35,36,38,41,42]	≥4	4,965/7,072 (70)	505 (10.2)	7.7	5.0-11.6
	<4	2,377/7,072 (34)	76 (3.2)	2.3	1.3-4.1
Ten studies, data at both 7 and 90 days[3,17,22,28,30,31,35,38,41,42]	≥4	2,824/4,443 (64)	189 (6.7)	5.2	2.8-9.4
	<4	1,572/4,291 (36)	29 (1.8)	1.4	0.7-3.1
At 90 days					
All studies (22/29)[3,9,15,17,22,25,26,28-35,37-39,41,42]	≥4	7,042/11,029 (64)	594 (8.4)	7.2	4.8-10.8
	<4	3,987/11,029 (36)	91 (2.3)	2.4	1.1-5.4
Ten studies, data at both 7 and 90 days[3,17,22,28,30,31,35,38,41,42]	≥4	2,824/4,443 (64)	281 (9.9)	8.9	5.3-14.5
	<4	1,619/4,443 (36)	44 (2.7)	2.4	1.3-4.4
At more than 90 days					
Three studies[16,24,34,40]	≥4	1,270/1,862 (68)	165 (13)	10.7	3.8-26.3
	<4	592/1,862 (32)	50 (8.4)	9.2	2.2-31.2

Figure 1 Proportion of patients with recurrent stroke by ABCD2 score (studies reporting 7- and 90-day stroke)



(A) ABCD2 ≥4, recurrent stroke at 7 days. (B) ABCD2 score ≥4 and recurrent stroke at 90 days. (C) ABCD2 score <4 and recurrent stroke at 7 days. (D) ABCD2 score <4 and recurrent stroke at 90 days.

1,443 patients with ABCD2 score ≥4 (p = NS). The proportion of patients with AF and ABCD2 score ≥4 (20%) was larger than those with ABCD2 score <4 (13%, p = 0.04). One study provided 90-day stroke rate, which was 3.4% in patients with ABCD2 score ≥4, 3.9% in patients with ABCD2 score <4 and carotid stenosis/other key risk factors, and 0.4% in patients with ABCD2 score <4 without these key risk factors.[9] Another study showed that recurrent stroke rate at 90 days increased with increasing carotid stenosis in patients with ABCD2 score ≥5.[48]

ABCD2 scores in TIA/minor stroke mimics. All except 3 studies[29,43,44] specifically excluded the cases diagnosed

as mimics by specialist neurologic examination. The 3 studies (2 retrospective, 1 prospective) provide data on 1,769/3,646 (48.5%),[43] 257/700 (36.7%),[44] and 79/713 (11%)[29] mimics. Low ABCD2 scores were associated with mimics; after dichotomization at ABCD2 0–1 or 0–2, the positive predictive value of ABCD2 score for a noncardiovascular diagnosis was 0.81 and 0.74, respectively.[43] In a prospective cohort,[44] mean ABCD2 scores were higher in patients diagnosed with minor stroke (4.9, SD 1.4) and TIA (3.9, SD 1.5) than in mimics (2.9, SD 1.5, $p < 0.00001$); ABCD2 score ≥4 increased the odds of a diagnosis of confirmed TIA (odds ratio [OR] 2.8; 95% CI 2.0–3.9; sensitivity 60.3% and specificity 64.6%) or minor stroke (OR 8.4; 95% CI 3.8–18.9; sensitivity 82.2% and specificity 64.6%) vs mimic. However, 18% of minor stroke and 39% of TIA patients had ABCD2 scores <4 and 35% or 41% of those with noncardiovascular diagnoses had ABCD2 score ≥4.[29,44]

ABCD2 scores and impact per 1,000 patients triaged. We calculated the expected number of recurrent strokes in a hypothetical cohort of 1,000 referrals to a stroke prevention clinic in patients with ABCD2 scores </≥4 using data from the 10 studies that provided data on stroke at both 7 and 90 days (table 2). We calculated the effect per 1,000 probable or definite TIA/minor strokes (i.e., after exclusion of mimics by expert clinical assessment as occurred in all studies): 635 of these patients, i.e., the majority, would be classed as ABCD2 ≥4 and require fast-track assessment. Among all patients referred including those with a final diagnosis of mimic, 520 would be classed as ABCD2 ≥4 and be fast-tracked. Table 2 demonstrates that 52% of the 1,000 clinic referrals including mimics would have an ABCD2 score ≥4, among whom would be 171 (30%) mimics. There were similar numbers of patients with carotid stenosis or AF between the high- and low-score groups. More recurrent strokes would occur in the ABCD2 ≥4 group, but about one fifth were estimated to occur among patients classed as low risk.

DISCUSSION Combined data from 29 cohorts, 13,766 patients, with TIA/minor stroke identified that the ABCD2 score is unlikely to perform as intended in clinical practice. Most studies included patients with definite (neurologist-determined) TIA and excluded patients with possible TIA or a mimic before applying the score, yet mimics constitute about half of clinic referrals. Where included, about a third of patients with a mimic had an ABCD2 score ≥4 and about one third of true TIA patients have a score <4.[43,44] The data do not support use of the ABCD2 score until after the patient has been confirmed as a definite TIA by a stroke specialist. However, as per its original purpose, use of the score by nonexperts is encouraged, including with financial incentives to fast-track patients with ABCD2 score ≥4 to clinics in some countries.[8] Nurses now perform initial patient triage in about 30% of TIA clinics using the ABCD2 score,[11] but several studies indicate that the agreement for ABCD2 scoring between nonspecialists and vascular neurologists is only fair,[12,49,50] and the score has low sensitivity and specificity when used by nonspecialists in the community[12] or emergency department,[34] irrespective of the cutpoint used.[50] These limitations[50] have led to withdrawal of recommendation of the ABCD2 score from the Canadian stroke guidelines.

The studies show that a consistently high proportion of patients had ABCD2 scores ≥4, indicating that the score is unlikely to have great impact on reducing workload in the hospital's fast-track channel. Studies that assessed different cutpoints, which we were therefore not able to include in our meta-analysis, did not find any better performance than we found for the <4/≥4 cut. For example, Perry et al.[50] tested cutpoints of >2 and >5 and found that the accuracy for predicting stroke risk when used by the enrolling physician or the coordinating center was poor (area under the curve 0.56; 95% CI 0.47–0.65

Table 2 Effect of the ABCD2 score per 1,000 patients triaged at stroke prevention services

ABCD2	Probable/definite TIA/minor stroke	Mimics	Total	Percent with key risk factors		Recurrent stroke	
				Carotid stenosis	Atrial fibrillation	<7 d	90 d
Population of 1,000 patients with probable or definite TIA							
≥4	635	0	635	15.4	20.2	30	52
<4	365	0	365	14.8	12.7	6	10
Population of 1,000 unselected clinic referrals including mimics							
≥4	349	171	520			16	27
<4	201	279	480			5	5

and 0.65; 95% CI 0.57–0.73, respectively). Meng et al.[24] obtained similar results on the same cutpoints. Cancelli et al.[17] found better ABCD2 score performance on these cutpoints in a population-based TIA incidence study, but all suspected TIAs were carefully assessed prospectively by expert neurologists.

Of concern, 1 in 5 patients with an ABCD2 score <4 have symptomatic carotid stenosis of >50% and need prompt treatment but, according to guidelines,[5] would be placed in the slow stream and incur delays to endarterectomy.[9,21,32,47] Given the well-established high risk of early recurrent stroke after TIA/minor stroke in patients with significant carotid stenosis,[48,51–53] it is unsurprising that adding carotid stenosis to the ABCD2 score improves stroke prediction.[54,55] Hence, refinements of the ABCD2 score to include etiologic variables such as carotid stenosis show improvement in the score's predictive power.[56] Similarly, including findings from brain imaging of recent ischemic lesion on diffusion-weighted MRI or CT scanning[55,57] identifies patients with active embolic sources and thus also improves predictive power.

Although many studies included in this work individually produced ROC curves suggesting that the ABCD2 score had good predictive value (table e-3),[7] the ABCD2 score evidence base has limitations. About half of studies identified patients retrospectively and about 42% determined the ABCD2 score retrospectively from case notes. Few studies reported what secondary prevention measures were used (endarterectomy, medical therapy), which makes assessment of the relation between ABCD2 and stroke rates difficult. Clinical setting, time of assessment from symptom onset, diagnosis of TIAs, and evaluating clinicians varied considerably across studies. Many studies did not differentiate recurrent disabling stroke from any recurrent stroke and some studies may have counted a recurrent TIA or progressing stroke as a stroke recurrence.

A recent systematic review and meta-analysis of ABCD2 scores and stroke risk (33 studies, 16,070 patients)[10] did not dichotomize on ABCD2 </≥4, included information only published in abstract, and did not identify the study methodology issues that we have highlighted. They concluded that "the ABCD2 score leads to only small revisions of baseline stroke risk particularly in settings of very low baseline risk and when used by nonspecialists," although most of their data came from specialists.

We were unable to test other ABCD2 cutpoints, but most data and guidelines refer to </≥4. We used tabular rather than individual patient data—while individual data might have allowed us to explore alternative cutpoints in more detail, they would not have overcome the fundamental problem in 48% of studies due to retrospective case ascertainment and assignment of the ABCD2 score and our results are consistent with smaller previous studies that did use individual data.[7,54] Strengths include comprehensive searching, literature assessment, and data assimilation. It is unlikely that we have overlooked any large relevant studies that would alter the conclusions.

Clinical implications. Dichotomizing the score on </≥4 does not reliably distinguish patients who need the most urgent intervention from those with mimics, and does not significantly reduce the workload on the limited capacity of a hospital's fast-track system. Guidelines that recommend urgent treatment only for patients with ABCD2 scores ≥4 while patients with low scores wait for up to a week[5] risk missing patients with risk factors that require specific prompt treatment. Patients with suspected TIA/minor stroke require urgent expert neurologic assessment to identify those with true TIA/minor stroke, identify key risk factors, and implement appropriate secondary prevention as fast as possible. The reliability and reproducibility of the ABCD2 score among nonexperts does not support its use by non-neurologically trained front-line staff; notwithstanding these concerns, there may be a role for its use where such expertise is not available.

Future research. There is a case for further methodologically rigorous work to assess the benefits and harms of the ABCD2 and other decision support tools on stroke prevention, prospectively in clinical settings where the tool will be used. Risk prediction tools should undergo the same standards of testing required in other fields such as therapeutic trials or epidemiology.

AUTHOR CONTRIBUTIONS

J.M. Wardlaw: concept, obtaining funding, design, evaluation of papers, interpretation of data, drafting and editing of paper, oversight of project, responsibility for the integrity of the data and the accuracy of the data analysis and overall guarantor of the work. M. Brazzelli: literature search, literature evaluation, data extraction, tabulation, editing of paper. F.M. Chappell: statistical analysis, creation of forest plots, editing of paper. H. Miranda: evaluation of literature, data extraction, tabulation of data, editing of paper. K. Shuler: data management, searching, data preparation, editing of paper. P.A.G. Sandercock: design, interpretation of data, editing of paper. M.S. Dennis: concept, design, editing of paper, interpretation of data.

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