

Clinical Prediction Rules to Stratify Short-Term Risk of Stroke Among Patients Diagnosed in the Emergency Department With a Transient Ischemic Attack

Kaushal H. Shah, MD
Hallie A. Metz, MD
Jonathan A. Edlow, MD

From the Department of Emergency Medicine, St. Luke's-Roosevelt Hospital, New York, NY (Shah); Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA (Metz, Edlow).

Study objective: Several clinical prediction rules have been created to help physicians stratify the risk of future stroke for a patient diagnosed with transient ischemic attack. We performed an evidence-based emergency medicine shortcut review of available prognostic scores to determine which clinical prediction rules are valid and useful. Can emergency physicians reliably use a clinical prediction rule to predict which transient ischemic attack patients assessed in the emergency department have a low enough risk of acute stroke (1% to 2%) to be discharged home and which have a sufficiently high risk so that hospitalization is the safest disposition?

Methods: We searched PubMed, EMBASE, and DARE database for articles that derived or validated a clinical prediction rule to stratify the risk of stroke up to 7 days among patients with transient ischemic attack. We used standard criteria to determine the level of development of the rule and to appraise the quality of various prognostic studies.

Results: Five studies met the inclusion criteria. Three clinical prediction rules were derived, the "California rule," the "ABCD rule," and the "ABCD² rule." The ABCD rule has been validated in multiple studies (level 2), with a consistent 7-day risk of stroke less than 2% for patients with scores of less than 4. The California rule has been validated in only 1 independent cohort (level 3). The ABCD² rule has only been internally validated using a split sample technique (level 4). In all 3 clinical prediction rules, a higher prognostic score correlates with increased risk in all the derivation and validation studies.

Conclusion: There is a clear and predictable increase in stroke risk with an increased number of risk factors in all 3 clinical prediction rules. The ABCD rule has been well validated and is most likely to be predictive and clinically useful. Patients with an ABCD score of less than 4 are clearly at lower risk of stroke within 2 and 7 days of presentation (<2%) and may be candidates for discharge home with urgent outpatient evaluation. Future research in this area should involve impact analysis of the ABCD rule and further validation of the California and ABCD² rules in other populations. [Ann Emerg Med. 2009;53:662-673.]

0196-0644/\$-see front matter

Copyright © 2008 by the American College of Emergency Physicians.
doi:10.1016/j.annemergmed.2008.08.004

CLINICAL SCENARIO

You are working an evening shift as the sole provider in a community hospital emergency department (ED) which has 24-hour neurology consultation coverage. At 9 PM, a 67-year-old woman is brought to the ED by her daughter, who says that while they were walking to their car after dinner her mother suddenly dropped the car keys from her right hand, had a right facial droop, and had "garbled" speech. The patient's daughter helped her into their car, where they sat for approximately 20 minutes before her speech and strength returned to normal. Now, approximately 60 minutes later in the ED, the patient says she feels fine and wants to go home. The patient's daughter says that although her mother has a history of high blood pressure, she has been otherwise healthy. The daughter is very concerned about her mother. She has never

seen her like that before and asks whether it is safe for her to go home after almost having a stroke.

At your hospital, the practice has been to admit all of the patients who present with a first-ever transient ischemic attack. However, you moonlight at another community hospital in the area that will frequently discharge patients home with a first-ever transient ischemic attack. This inconsistency has always concerned you. Is there a way to reliably determine which patients are at highest risk of stroke in the near future and cannot be discharged home safely? Conversely, are there other patients so unlikely to have a stroke that they can be safely discharged with follow-up with a neurologist within a few days as an outpatient? The following evidence-based review seeks to answer the questions raised by this clinical scenario for both the physician and the patient.

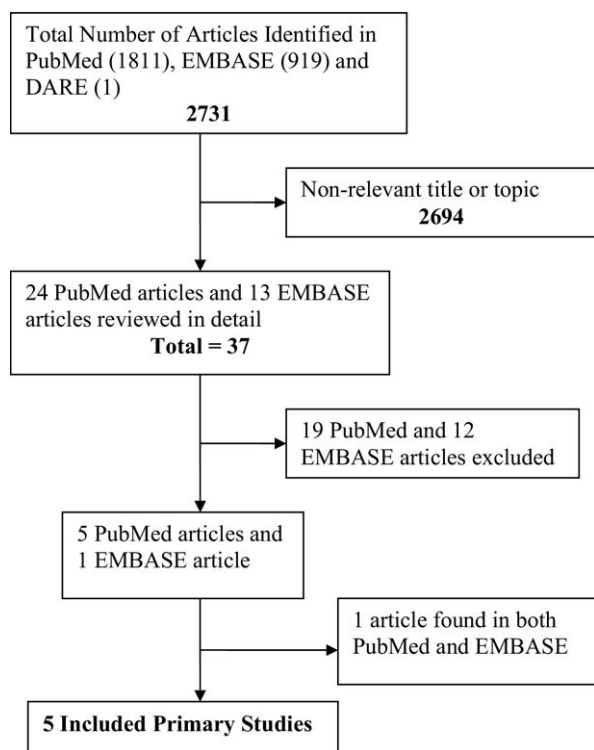


Figure. Process of selecting included studies (completed July 31, 2007).

FORMULATING THE QUESTION

Recent data suggest that the short-term risk of stroke (as high as 5% in 2 days and 7% in 7 days) in patients with transient ischemic attack is substantially higher than previously thought.¹⁻³ The period of short-term risk of stroke that is most relevant to emergency physicians is probably the first week after presentation to the ED.³ Patients at high early risk of stroke may benefit from admission to the hospital for further evaluation and treatment, whereas those at low risk may prefer to be discharged to undergo an expedited outpatient evaluation.

Although neither was a randomized clinical trial, data from 2 recent independent studies using different methods compared immediate evaluation in clinics with continuous access and no appointment needed to conventional care.^{4,5} Both studies found an 80% reduction in acute stroke when transient ischemic attack patients underwent immediate evaluation and initiation of treatments such as anticoagulation and carotid interventions. These same steps might also be undertaken in an ED-based observation unit.⁶ It is not the hospitalization per se that confers this risk reduction, but the rapidity of the evaluation; in most hospitals, this rapid evaluation could occur only with an admission. Currently, there is no clear-cut standard practice because 50% of transient ischemic attack patients are discharged home from United States EDs.^{7,8}

A “prediction rule” is a way of organizing prognostic information into a quantitative form and does not actually determine a course of action. However, a reliable clinical

prediction rule would provide the best available information to allow the physician and patient to discuss the appropriate treatment and disposition. In this case, the clinical prediction rule would risk stratify an individual transient ischemic attack patient’s risk of stroke, thereby forming a basis for a collective decision and course of action. Regardless of what level of risk a patient is “predicted” to have, there will be extenuating circumstances that alter the application of the clinical prediction rule, such as a “low-risk” patient without adequate access to outpatient care who may prefer to be admitted or a “high-risk” patient who insists on going home and seeing the physician the very next morning.

Our goal was to assess existing clinical prediction rules for estimating an individual transient ischemic attack patient’s short-term risk for stroke.

Because there is some controversy about the best definition of transient ischemic attack, we wanted to be specific in formulating the question. The classic definition of transient ischemic attack is a neurologic deficit caused by focal brain ischemia that completely resolves within 24 hours. With the increased availability of sophisticated imaging modalities such as magnetic resonance imaging and a treatment for stroke that must be administered within 3 hours of symptom onset, this traditional definition of transient ischemic attack has been questioned.⁹ A new proposed definition by the TIA Working Group is “a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction.”¹⁰ Because the new proposed definition is not universally accepted, we used the classic definition of transient ischemic attack in our review and search.

We also used the standard clinical definition of stroke: a neurologic deficit due to focal brain ischemia that lasts more than 24 hours. Stroke is a clinically relevant outcome that is of obvious importance to patients and their families. It has been estimated that 1 in 3 stroke survivors need help caring for themselves, and 1 in 5 need help walking. Seven of 10 cannot return to their previous jobs, and 51% are unable to return to any type of work after stroke.¹¹ In addition, 11% to 18% of strokes are fatal.¹² Recent data suggest that expedited diagnostic evaluation and intervention in transient ischemic attack patients can markedly reduce the outcome of stroke.^{4,5}

The application of the various clinical prediction rules may vary according to the population to which they are applied. To assist emergency physicians in their decisionmaking, we wanted to determine how the clinical prediction rule performed in the acute care setting. Although we prefer the clinical prediction rule to be applied to patients evaluated specifically in the ED by emergency physicians, we did not want to be overly focused and too narrow in formulating the question.

The cause and natural course of transient neurologic symptoms (and the course of the disease) are likely to be different between adults and children. Because the majority of

Table 1. Description of clinical prediction rules.

Hierarchy of Evidence ¹³	CPR	Factors Included	Score
Level 3	California rule	Age \geq 60 years	1
		Diabetes	1
		Unilateral weakness	1
		Speech Impairment	1
		Symptom duration >10	1
		Total possible points	5
Level 2	ABCD rule	Age \geq 60 years	1
		Elevated BP	1
		Systolic >140 mm Hg	
		Diastolic >90 mm Hg	
		Unilateral weakness	2
		Speech impairment without unilateral weakness	1
		Symptom duration, min	
		\geq 60	2
		10–59	1
		<10	0
Total possible points	6		
Level 4	ABCD ² rule	Age \geq 60 years	1
		Elevated BP	1
		Systolic >140 mm Hg	
		Diastolic >90 mm Hg	
		Unilateral weakness	2
		Speech impairment without unilateral weakness	1
		Symptoms duration, min	
		\geq 60	2
		10–59	1
		<10	0
Diabetes	1		
Total possible points	7		

CPR, Clinical prediction rule; BP, blood pressure.

patients presenting to the ED with transient ischemic attacks are adults,⁸ we limited the study question to adults only.

The final consideration in formulating the question entails how “low” does the short-term risk need to be to affect the clinical decision. Is there a threshold risk below or above which it is acceptable to discharge a patient from the ED or recommend admission to the hospital? The amount of risk a patient or physician is willing to tolerate varies, and as such an exact number is not possible. Certainly, a clinical prediction rule that predicts 0% risk would be ideal; however, rules with such performance characteristics are rare in medicine. We hypothesize that a 1% to 2% risk of stroke after a transient ischemic attack would be a reasonable basis for discussion of discharge between emergency physicians and patients.

We formulated our question as, can emergency physicians reliably use a clinical prediction rule to predict which transient ischemic attack patients assessed in the ED have a low enough risk of acute stroke (1% to 2%) to be discharged home and which have a sufficiently high risk to recommend hospitalization as the safest disposition?

Searching for and Selecting the Best Evidence

The normal sequence to develop a clinically useful clinical prediction rule is to derive the “rule” by making a list of

potential predictors of the outcome and then studying a group of patients and determining whether the clinical predictors are present.¹³ Because the effect of clinical predictors may vary across different populations and individuals and because there is variation in the hands of different practitioners who apply them, a rule that has only been derived needs to be validated in at least 1 cohort of patients that is independent from the patients used to derive the rule before it can be recommended for even limited use by clinicians in making decisions for their own patients.¹³ In some cases, a derivation and a validation set can be reported in a single article (provided it meets the above specifications). Frequently, however, validation studies are done and reported by different investigators. After performance validation, studies are done to determine the true influence of a validated rule, termed “impact validation” studies. It is at this stage that the actual effect on decisionmaking of prediction rules aimed at stratifying the risk of clinical outcomes can be assessed.

We sought to include studies reporting either the derivation or the validation of clinical prediction rules for determining individual risk of stroke after a transient ischemic attack. Derivation studies were included primarily for purposes of comparison and completeness only. Assessment of whether the clinical prediction rule can or should be used in the clinical setting will be based on the validation studies.

Table 2. General study information.

CPR	Study	Patients	Individual Predictors/ Rule	Outcomes Reported	Study Design
California	Johnston et al, 2000 (derivation study) ¹⁶	1,707 adult ED patients from Northern California Kaiser-Permanente with a primary diagnosis of TIA. Data gathered during 1-year period to determine outcome at 90 days. All patients identified with TIA by ED physician.	5 factors associated with stroke: Age >60 year Diabetes Symptom duration >10 minutes Unilateral weakness Speech impairment	Primary outcome: Risk of stroke from 2 to 90 days after index TIA. Secondary outcomes: death, recurrent TIA, and hospitalization for cardiovascular events.	Derivation study based on retrospective chart review
ABCD	Rothwell et al, 2005 (derivation and validation study) ²⁰	Derivation group: 209 adult patients with first ever TIA in the OCSF. Data collected during 5-year period. Followed for 1 month. Validation groups: 1. 190 Adult patients with first-ever TIA in OXVASC. 2. 210 Adult patients referred to Hospital clinics with suspected or probable TIA. All patients assessed by study neurologist, followed up at 1 month and reassessed by neurologist. All data collected during 2-year period.	6-Point score: Age ≥60 year Blood pressure >140/90 mm Hg Clinical features (unilateral weakness and speech disturbance) Symptom duration	Derivation of prediction rule (ABCD score) for risk of stroke during the 7 days after index TIA. Validation of prediction rule.	Derivation and independent validation
	Tsivgoulis et al, 2006 (validation study) ²¹	238 consecutive patients hospitalized during 5-year period with a diagnosis of definite TIA. All patients presenting to the ED of the neurology department primarily screened by the attending neurologist.	6-Point score, as above	7- and 30-day stroke risk applied to ABCD prediction rule at each cutoff score	Retrospective validation
	Bray et al, 2007 (validation study) ²²	102 adult ED patients during 6-mo period in Melbourne, Australia, with first ever TIA. Follow-up by medical record review, telephone inquiry within 90 days of admission after TIA.	6-Point score, as above	Stroke risk at 7 and 90 days with respect to dichotomized ABCD score (high risk is score ≥5)	Retrospective validation
ABCD ²	Johnston et al, 2007 (derivation study) ¹⁹	4,809 combined adult ED and clinic patients with TIA in United States and United Kingdom. Retrospectively validated California and ABCD scores for prediction of 2-day stroke risk after TIA in same populations as initially used, as well as 4 new individual patient groups. Derived composite clinical decision rule for 2-day stroke risk, ABCD ² , applied that rule in the same patient groups.	California rule and ABCD rules as above, plus new rule ABCD ² score: Age Blood pressure Clinical features Duration of symptoms Diabetes	Risk of stroke at 2, 7, and 90 days after TIA presentation stratified by ABCD ² score using previously published data sets	Validation of California and ABCD rules Derivation of modified rule with split sample to control for random error within component data sources.

TIA, Transient ischemic attack; OCSF, Oxfordshire Community Stroke Project; OXVASC, Oxford Vascular Study.

Table 3. Hierarchy of evidence for clinical prediction rules.¹³

Level of Evidence	Application	Requirements
Level 1	Can be used in a wide variety of settings with confidence that they can change clinical behavior and improve patient outcome	At least 1 prospective validation and 1 impact analysis demonstrating change in clinical behavior with beneficial consequences
Level 2	Can be used in various settings with confidence in their accuracy	Demonstrate accuracy in either 1 large prospective study or validated in several smaller settings
Level 3	Clinicians may consider using with caution and only if the patients in the study are similar to those in the clinician's setting	Validated in only 1 narrow prospective sample
Level 4	Need further evaluation before they can be applied clinically	Derived but not independently validated

The best evidence for validation of a clinical prediction rule is from prospective studies. They are best suited to demonstrate the potential effect of a consistently performing prediction rule on clinical practice. Application of clinical prediction rule criteria retrospectively is far less reliable.

We considered all articles in which patients presented with transient ischemic attack symptoms to an acute care setting including EDs, urgent care clinics, and general practitioners; however, the best evidence for our study question will clearly come from the study of patients presenting to the ED.

Presuming that the typical practitioner's approach to the care of a patient with history of transient ischemic attack or stroke would be significantly different from their approach to a patient without a history of symptoms, we ideally wanted to focus on studies centered on patients presenting with a first-ever transient ischemic attack. We did not, however, limit the search to first-ever transient ischemic attack for fear of being overly narrow in study selection.

Our primary focus in searching for literature was on studies reporting the risk of stroke within 2 to 7 days of index transient ischemic attack and those that developed clinical prediction rules for determining which patients are at highest risk of stroke. However, because the majority of older literature addresses the 30-day stroke risk after transient ischemic attack, we used this longer period for selecting evidence to more reliably capture all relevant studies.

The diagnosis of transient ischemic attack has historically been challenging, with a high level of interobserver disagreement, even among neurologists who are not frequently involved in the initial evaluation process.^{14,15} One large study found that the diagnosis of transient ischemic attack made in the ED by emergency physicians is reasonably accurate, as measured against a neurologist's review of the chart.¹⁶ We therefore concentrated on studies in which transient ischemic attack diagnosis was made in the acute care setting by an emergency physician or a neurologist.

There is no current consensus for the disposition of patients presenting with index transient ischemic attack to the ED in the United States health care system. Recommendations for

appropriate hospital admissions and approach to evaluation of these patients varies greatly, leading to a broad diversity in practice.^{7,8,17} A prognostic score that determines an individual patient's risk of stroke would vastly help patients, their families, and emergency physicians make the most informed decision with respect to risk. We therefore focused on studies that derived and, especially, validated a prognostic scoring tool to predict an individual patient's risk of impending stroke, which could then be applied to making a decision on disposition from the ED. For example, does the patient in our scenario fall into a "low enough" risk group (sufficiently small chance of stroke in the next week) such that the patient, daughter, and emergency physician can feel comfortable that an outpatient evaluation confers a low enough risk of near-term stroke to be discharged from the ED?

We excluded studies not conducted in an acute care setting because the cohort of patients that present weeks after symptom onset is logically a different population than the group that presents acutely. Studies that focused only on patients with known history of transient ischemic attack or stroke were also excluded because the therapeutic approach to these patients would likely differ because the suspicion for recurrent transient ischemic attack or stroke would be much higher in these patients.

We searched 3 databases (PubMed, EMBASE, and DARE) for studies that reported the incidence of stroke after transient ischemic attack by not limiting the definition of prognosis, outcome, or prediction. In the case of derivation and performance validation studies, we looked for cohort studies that would, ideally, be done prospectively. However, we also decided to include studies done retrospectively while keeping in mind that the highest level of evidence will come from prospective applications of the rule.

In PubMed, we combined the following free-text terms: ("TIA" OR "transient ischemic attack") AND ("stroke" OR "CVA" OR "cerebral vascular accident") and ("score" OR "prediction" OR "prognosis" or "risk"). After limiting this search to the English language, adults (≥ 19 years), and humans, the database yielded 1,811 results on July 31, 2007 (full search

Table 4A. Critical review.

CPR	Study	Are Enrolled Patients Representative of ED Population?	Well-Defined Sample of TIA Patients? Properly Diagnosed?
California	Johnson et al, 2000 (derivation study) ¹⁶	Yes—Population base of 2.9 million enrollees visiting 16 hospitals of HMO (Kaiser-Permanente) in Northern California and diagnosed in the ED.	Yes—Patients diagnosed with TIA by emergency physician Yes—Neurologists blinded to outcomes reviewed medical record of all patients in whom diagnosis of TIA was unclear
ABCD	Rothwell et al, 2005 (derivation and validation study) ²⁰	No—OCSP, OXVASC, and hospital clinic populations were patients presenting to family physicians in England	Yes—Patients diagnosed with TIA by neurologist using the same definition
	Tsivgoulis et al, 2006 (validation study) ²¹	Partially—All patients presented to the ED but study completed in inpatient setting. There appears to be a selection bias because patients discharged with a TIA diagnosis were not included; only admitted patients were enrolled.	All patients were evaluated by a neurologist on presentation to the ED
	Bray et al, 2007 (validation study) ²²	Yes—All patients presented to the ED. Diagnosis made by emergency physician	Not well described. All initial diagnoses made by physician in ED. Neurology consulted on 45% cases. Patients selected from retrospective review of medical records by research nurses as quality assurance audit of patients with TIA.
ABCD ²	Johnston et al, 2007 (derivation study) ¹⁹	Patients are from a variety of settings. The patients from the California EDs and the hospital-based Oxfordshire TIA clinics are representative of an ED population. However, OCSP, OXVASC, and hospital clinic populations are patients presenting to family physicians in England	Yes—All patients diagnosed with TIA by initial treating physician. Diagnosis confirmed by study neurologist.

strategy is reproduced in [Appendix E1](#), available online at <http://www.annemergmed.com>). After review of the titles and abstracts for clear exclusion criteria, 24 articles were identified for detailed review ([Figure](#)).

In EMBASE and DARE (Cochrane library's database of abstracts of reviews of effects), we searched for appropriate articles, using combinations of the following terms: "transient ischemic attack," "tia," "stroke," "cerebrovascular accident (cerebrovascular or cerebral vascular accident)," "cva," "score," "predict," "prognosis," and "risk." EMBASE yielded 919 results and DARE yielded 1 result on July 27, 2007. After review of these articles for clear exclusion criteria in either the title or abstract, 13 articles from the EMBASE search were identified for detailed review. The one article identified in DARE was excluded.

Two authors (H.A.M. and J.A.E.) independently reviewed 24 articles through the PubMed database and 13 articles through EMBASE to determine inclusion in the review. Inclusion criteria were (1) adults, aged 19 years or older, (2)

diagnosis of transient ischemic attack, (3) evaluation in an acute care setting, (4) outcome of stroke within 7 days of presentation of index transient ischemic attack, (5) prediction, and (6) derivation or validation studies. With 100% concordance, 5 articles in the PubMed database were included; 19 were excluded. One article from the EMBASE database was included and 12 were excluded. The included EMBASE article was also identified and selected from the PubMed search. One prospective validation of the ABCD rule was excluded because it reported only stroke outcome at 90 days.¹⁸ Five articles were selected for analysis at the completion of the search process.^{16,19-22} One additional article²³ was discovered after our literature search was complete that attempted to identify factors associated with stroke recurrence after an "initial minor stroke or transient ischemic attack" in a prospective hospital series. The study did not qualify for inclusion because it enrolled only patients with a diagnosis of acute ischemic stroke, and the authors self-reported the inability to validate any models because of their methodology.

Table 4B. Critical review.

CPR	Study	Are Patients at Similar Points in Disease?	Objective and Unbiased Outcome Criteria?	Were Predictors Present in a Significant Proportion of the Study Population?
California	Johnson et al, 2000 (derivation study) ¹⁶	99% of patients presented within 1 day of symptoms, 26% with previous TIA and 23% with previous stroke	Diagnosis required independent confirmation by 2 neurologists (who reviewed the charts). Standard criteria for stroke diagnosis	Yes: Age ≥60 year (78%) Diabetes (19%) Symptoms >10 min (84%) Unilateral weakness (46%) Speech impairment (52%)
ABCD	Rothwell et al, 2005 (derivation and validation study) ²⁰	Unclear, does not give detail of time between onset and evaluation in either OCSP or OXVASC study. All patients with first-ever TIA.	Not well described. Diagnosis of first-ever TIA made in outpatient environment confirmed by study neurologist. Standard criteria for diagnosis. Same criteria used in derivation and validation. Study sponsor had no role in design, collection, analysis, interpretation, or writing.	Yes: <u>OCSP derivation population:</u> Age ≥60 year (12%) HTN (38%) Unilateral weakness (54%) Speech disturbance (13%) Symptoms >60 min (36%), 10–59 min (30%), <10 min (33%) <u>OXVASC validation population:</u> Age ≥60 y (12.5%) HTN (53%) Unilateral weakness (50%) Speech disturbance (22%) Symptoms >60 min (51%), 10–59 min (33%), <10 min (16%) <u>Hospital clinic validation population:</u> Age ≥60 year (12.5%) HTN (52%) Unilateral weakness (38%) Speech disturbance (21%) Symptoms >60 min (51%), 10–59 min (29%), <10 min (21%)
	Tsivgoulis et al, 2006 (validation study) ²¹	Symptom onset to hospital admission <48 h in all cases and 87.6% within 24 h. 35% had TIA in the preceding month.	Yes—well-defined stroke definition.	Yes: Age ≥60 year (61.5%) HTN (56.6%) Unilateral weakness (46.5%) Speech disturbance (42.5%) Symptoms >60 min (46.5%), 10–59 min (36.7%), <10 min (16.8%)
	Bray et al, 2007 (validation study) ²²	Median time from onset of symptoms to presentation to ED was 135 min (25 min to 48 h). Did not specify whether patients had previous TIA or first-ever TIA.	Retrospective review of medical records by research nurses as quality assurance audit of patients with TIA. Multiple methods used to reduce bias.	Yes: Age ≥60 year (79%) HTN (73%) Unilateral weakness (57%) Speech disturbance (19%) Symptoms >60 min (79%), 10–59 min (9%), <10 min (12%)
ABCD ²	Johnson et al, 2007 (validation study) ¹⁹	Unclear. Some patients described as presenting within 1 day of index TIA; others described only as presenting shortly after TIA. Did not specify whether patients had previous TIA or first-ever TIA.	Retrospective review of previously gathered data for validation of early scores. Newly derived score from independent retrospectively gathered data sets using multivariable regression analysis. Results confirmed in each of the 4 component data sets.	Yes: Age ≥60 year (77%) HTN (71%) Unilateral weakness (41%) Speech disturbance (19%) Symptoms >60 min (62%), 10–59 min (21%) Diabetes (17%)

HTN, Hypertension.

ANALYZING THE EVIDENCE

Description of the Studies

Table 1 describes each clinical prediction rule, specifically, the factors that compose the clinical prediction rule and their numeric weight. Table 2 summarizes the key features of the studies selected for review.

The Johnston et al¹⁹ study is complex and requires a more explicit description. The study analyzed the previously collected data from 2 earlier studies, Johnston et al¹⁶ and Rothwell et al,²⁰ and retrospectively validated their derived prediction rules (“California rule” and the “ABCD rule,” respectively) in a number of independent data sets. Johnston

Table 5. Rule-based outcomes.

CPR	Study	Number of Stroke Risk Factors	Stroke Outcome: 2 Day, (95% CI)*	Stroke Outcome: 7 Day, (95% CI)*	
California	Johnston et al, 2000 (derivation study) ¹⁶	0	Not available	Not available	
		1			
		2			
		3			
		4			
	Johnston et al, 2007 (validation study) ¹⁹	0	0 (0.0–5.4)	0 (0.0–5.4)	
		1	1.0 (0.4–2.5)	1.2 (0.5–2.8)	
		2	1.8 (1.2–2.9)	2.9 (2.0–4.1)	
		3	4.6 (3.5–6.4)	7.5 (6.0–9.3)	
		4	6.8 (4.8–9.5)	10.0 (7.6–13.1)	
	ABCD	Rothwell et al, 2005 (validation study: OXVASC population) ²⁰	≤1	Not available	0 (0.0–70.1)
			2		0 (0.0–14.3)
			3		0 (0.0–12.7)
			4		2.2 (0–6.4)
			5		16.3 (6.0–26.7)
6				35.5 (18.6–52.3)	
Rothwell et al, 2005 (validation study: hospital clinic population) ²⁰		≤1	Not available	0 (0.0–20.7)	
		2		0 (0.0–11.5)	
		3		0 (0.0–10.4)	
		4		9.1 (1.5–16.7)	
		5		11.8 (0.9–22.6)	
		6		23.8 (5.6–42.0)	
Tsvigouliset et al, 2006 (validation study) ²¹		0	Not available	0 (0.0–48.9)	
		1		0 (0.0–28.2)	
		2		0 (0.0–17.6)	
	3		1.7 (0–5.1)		
	4		7.6 (1.2–14.0)		
	5		19.1 (7.8–30.4)		
Bray et al, 2007 (validation study) ²²	0	Not available	0 (0.0–83.3)		
	1		0 (0.0–44.3)		
	2		0 (0.0–40.4)		
	3		0 (0.0–18.2)		
	4		0 (0.0–23.9)		
	5		10.7 (2.9–28.0)		
Johnston et al, 2007 (validation study) ¹⁹	0	0 (0.0–9.4)	0 (0.0–9.4)		
	1	1.0 (0.0–3.8)	1.0 (0.0–3.8)		
	2	1.4 (0.7–2.8)	1.6 (0.8–3.1)		
	3	1.3 (0.8–2.4)	1.6 (0.9–2.7)		
	4	3.4 (2.5–4.6)	5.0 (3.9–6.4)		
	5	6.1 (4.7–7.8)	8.3 (6.7–10.3)		
ABCD ²	Johnston et al, 2007 [†] (derivation study) ¹⁹	≤1	0 (0.0–2.2)	0 (0.0–2.2)	
		2	1.4 (0.6–3.0)	1.7 (0.8–3.3)	
		3	1.3 (0.7–2.4)	1.5 (0.9–2.7)	
		4	3.8 (2.8–5.1)	5.5 (4.3–7.0)	
		5	5.1 (3.8–6.7)	7.2 (5.7–9.0)	
		6	8.8 (7.0–10.9)	12.3 (10.2–14.7)	
		7	6.3 (3.3–11.3)	10.6 (6.7–16.4)	

CI, confidence interval.

*95% CI as reported or calculated using <http://graphpad.com/quickcalcs/ConfInterval1.cfm>.†ABCD² score was applied to 2 “derivation” groups and 4 “validation” groups in this study; because we believe it was a split sample (and not a true validation), the percentages presented are based on a combination of all 6 groups.

et al¹⁹ then derived a composite clinical prediction rule, the “ABCD² rule,” using a pooled data set independently and retrospectively drawn from patient populations involved in the development of the predecessor, California and ABCD rules. The derivation of the California score¹⁶ included diabetes as a risk factor. The derivation and validation of the ABCD score²⁰ did not use diabetes but did use increased blood pressure. These 2 studies were combined to create the composite ABCD² rule, which included all of the previously determined risk factors. All of the scores were analyzed among the same 4 validation populations to determine both 2- and 7-day stroke risks. They then report performance data of the ABCD² rule on each of the component data sources in a unique form of “split-sample” validation. Because all of the “validation” cohorts were already included in the population from which the rule was derived, this split-sample validation of the ABCD² rule controls only for random error within the derivation and does not demonstrate that the rule would hold up in an independent population. However, because 6 of the 7 points for this score are identical to the ABCD rule, it is possible that it would perform similarly well.

Susceptibility to Bias of the Studies

There are 2 distinct levels of evaluation of clinical prediction rules. There are well-established methodologic standards for evaluating the level of development of the rule (Table 3)¹³ and separate standard evidence-based medicine criteria to appraise the quality of the individual studies contributing to the development of the rule.

The hierarchy of evidence for each clinical prediction rule was graded on levels 1 to 4 (Table 1). None of the clinical prediction rules have undergone impact analysis and demonstrated change in clinical behavior with beneficial consequence (level 1). The ABCD rule has been validated in multiple studies and was assigned a level 2 rating. The ABCD² rule has not been validated in other than a split sample and therefore obtains the lowest rating of 4.

Tables 4A and B are a critical review of the individual prognostic studies and an assessment of the likelihood of bias in the 5 studies; appraisal questions are based on the fact that they are all cohort studies (randomized trials would require different appraisal criteria).

Johnston et al¹⁶ conducted a large study of transient ischemic attack patients presenting to the ED and derived the “California rule” from univariate analysis followed by a multivariate regression. This was a retrospective study.

Rothwell et al²⁰ derived and validated their ABCD score in the same population, but it was not a split sample. The 2 different cohorts were enrolled 14 years apart. A limitation of the Rothwell et al²⁰ study is that patients presented to family physicians and there is no detail of time between onset and evaluation. Therefore, these cohorts may not be representative of an ED population. However, the patients were all “first-ever” transient ischemic attack presentations and the diagnosis was confirmed by a study neurologist.

Although Tsivgoulis et al²¹ included patients who were diagnosed with transient ischemic attack by a neurologist and they likely presented to the ED of their neurology department, the patients were enrolled retrospectively according to hospitalization records. Patients discharged from the ED with a diagnosis of transient ischemic attack were not included, thus introducing a clear selection bias. Follow-up was excellent, with only 5 of 238 patients lost to follow-up. Because this study followed only patients who were admitted to the hospital after their initial presentation, this likely represents a population with more severe transient ischemic attack and would be expected to overestimate short-term stroke risk.

Although their validation study was retrospective, Bray et al²² used many measures to minimize bias: experienced abstractor, clear inclusion and exclusion criteria, clear extraction points for data collection, random independent review of data, and a predetermined plan for missing data. In addition, all included patients presented to an ED where an emergency physician made the diagnosis of transient ischemic attack, and only 4 of 102 patients were lost to follow-up. The overall number of enrolled patients in the cohort was low, with only 4 patients sustaining a stroke; therefore, the confidence intervals around the results are particularly wide.

Johnston et al¹⁹ used data from 2 earlier studies, both included in this review (Johnston et al¹⁶ and Rothwell et al²⁰), so the inherent biases in those studies apply to this article as well. The unifying factor of the included data was that confirmation of the initial transient ischemic attack diagnosis was determined by a study neurologist.

Primary Results

With respect to level of evidence, the ABCD rule received a level 2 rating (the highest among the 3 clinical prediction rules) because it was validated in multiple studies but has not had impact analysis. The California rule has been validated in only 1 study (level 3); therefore, clinicians can consider using it with caution if their patient population is similar to that in the Northern California Kaiser-Permanente system. The ABCD² rule received the lowest rating (level 4) because it has been derived and validated only in a split sample; it is not considered ready for clinical use.

The quality assessment of the individual studies is detailed in Tables 4A and B. The outcomes of the 3 clinical prediction rules (California rule, ABCD rule, and ABCD² rule) and their corresponding short-term risk of stroke after transient ischemic attack, including 2- and 7-day stroke risk, are reported in Table 5 and the Critically Appraised Topic (CAT) table. All the studies demonstrate increased stroke risk, with higher scores for all 3 clinical prediction rules.

Among the 4 studies that attempted to validate the ABCD score, the risk of stroke was reliably less than 2% (range 0% to 1.7%) at days 2 and 7 if the score was less than 4. At scores of 4 or greater, the risk of stroke increased to 5.4% at 2 days (Johnston et al¹⁹) and ranged from 6.3% to 13.2% at 7 days.¹⁹⁻²²

Neither of the original derivation studies, Johnston et al¹⁶ and Rothwell et al²⁰, applied their derived clinical prediction rules to determine 2-day stroke risk. For the validation of the ABCD rule, in the later Johnston study,¹⁹ patients with scores of less than 4 had less than a 1.5% 2-day stroke risk. As with the data above for a 7-day stroke risk, the higher the score, the higher the stroke risk. Patients with an ABCD score of 5 and 6 had a 6.1% to 7.7% 2-day stroke risk. This same trend of higher risk associated with a higher score was true of the California rule, as well as for the unvalidated composite ABCD² rule (Table 5). Authors of the ABCD² study suggested that patients with a score of 4 or higher might benefit from an admission to the hospital.¹⁹

APPLYING THE EVIDENCE

Returning to our clinical scenario of the 67-year-old woman who presented after a 20-minute transient ischemic attack, there are a few important things to consider: the risk of stroke as the outcome of interest, the ease of use, reliability, and effectiveness of our prediction rule, as well as the patient's perspective and psychosocial situation. The evidence from this review is clearly applicable to this patient because she presented to an ED and was treated by an emergency physician who diagnosed her with a transient ischemic attack. The elements of the ABCD score are clear cut and readily available in the ED. Our patient's risk factors are worrisome. She is older than 60 years, has a history of hypertension, presented both with unilateral weakness and speech disturbance, and had symptom duration between 10 and 60 minutes. Her ABCD score is 5, placing her in the high-risk group for impending stroke, with a 2-day risk of stroke of 6%¹⁹ and a 7-day stroke risk of 8% to 19%. With that level of risk, an immediate evaluation and initiation of treatment is the disposition that will result in the lowest risk of a near-term stroke.^{4,5} In many, if not most, facilities in the United States, this would require a hospital admission.

If the patient had an ABCD score of 3 or less, her risk of stroke in the next 2 to 7 days would be less than 2%. A very different discussion could take place. The patient may be comfortable with less than 2% as a "low enough" risk of short-term stroke occurrence, especially if she has an established primary care provider who can facilitate further evaluation as an outpatient.

Although the ABCD² rule has not been independently validated,¹⁹ the patient in our scenario would still fall in the intermediate group (score of 4 to 5), giving her a 2-day stroke risk of 4%. Validating the ABCD² rule will be a fertile area for future research because it may prove to be more generalizable, given that it was derived from a broader population and incorporates an additional risk factor (7-point composite score). Another potential predictor is adding the results of brain imaging to the various clinical variables, which may also be useful to further refine these clinical prediction rules.²⁴ Last, it will be important to perform "impact validation" studies to determine whether routine use of these clinical prediction rules actually improves clinical outcomes and avoids unnecessary

hospital admissions in practice to prove that using a clinical prediction rule in routine practice actually improves clinical outcomes.

Clearly, the patient's perspective must be considered. Ultimately, each patient should be approached on a case-by-case basis, and decisions need to be made with the patient's best interest in mind and in compliance with local institutional protocols. Discharging a patient implies that the patient and the system have the resources to conduct an expedited outpatient evaluation within days, which is not always the case. For example, organizing a timely evaluation in a patient without a primary care provider will likely be difficult.

PATIENT COMMUNICATION

Cerebrovascular disease has become a "hot topic" in recent years in the American Heart Association and other medical organizations, as well as the lay press. Patients are becoming better educated about transient ischemic attack and stroke and will have increasing need to understand the rationale for the medical decisionmaking for their care. The following is an example of how an emergency physician might convey the relevant information to a patient presenting to the ED with a transient ischemic attack, such as our patient and her daughter.

"I believe you had what is called a TIA or transient ischemic attack, a temporary disruption of blood flow to a portion of the brain, causing transient neurologic symptoms that have completely resolved. This means that for a short amount of time, the portion of your brain that controls your speech and the right side of your body was not receiving enough blood flow. The same things that cause strokes also cause TIAs, which are a warning sign of future stroke. Recent research allows us to estimate which patients are at highest risk of an impending stroke in the next few days by considering factors such as age, blood pressure, and the behavior of specific symptoms. These same criteria also allow us to identify patients at relatively low risk for such events. A stroke is different from what you have experienced because it may result in permanent disability or even death. If you fall into the higher-risk group, you may have up to 5 chances in a hundred of having a stroke in the next week. If your risk is low, it may be only 1 in a hundred or lower. We recognize that you may be more or less concerned about this kind of risk and would be inclined to offer you a short hospital stay, particularly because your risk is high."

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

Publication date: Available online October 11, 2008.

Reprints not available from the authors.

Address for correspondence: Kaushal Shah, MD, Department of Emergency Medicine, St. Luke's-Roosevelt Hospital, 1111 Amsterdam Ave, New York, NY 10025; 646-369-2747; 646-369-2747; Fax 212-523-2186; E-mail kshah@chpnet.org.

REFERENCES

- Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2007;6:1063-1072.
- Wu CM, McLaughlin K, Lorenzetti DL, et al. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:2417-2422.
- Shah KH, Kleckner K, Edlow JA. Short-term prognosis of stroke among patients diagnosed in the emergency department with a transient ischemic attack. *Ann Emerg Med*. 2008;51:316-323.
- Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet Neurol*. 2007;6:953-960.
- Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370:1432-1442.
- Ross MA, Compton S, Medado P, et al. An emergency department diagnostic protocol for patients with transient ischemic attack: a randomized controlled trial. *Ann Emerg Med*. 2007;50:109-119.
- Coben JH, Owens PL, Steiner CA, et al. Hospital and demographic influences on the disposition of transient ischemic attack. *Acad Emerg Med*. 2008;15:171-176.
- Edlow JA, Kim S, Pelletier AJ, et al. National study on emergency department visits for transient ischemic attack, 1992-2001. *Acad Emerg Med*. 2006;13:666-672.
- Shah KH, Edlow JA. Transient ischemic attack: review for the emergency physician. *Ann Emerg Med*. 2004;43:592-604.
- Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack—proposal for a new definition. *N Engl J Med*. 2002;347:1713-1716.
- Black-Schaffer RM, Osberg JS. Return to work after stroke: development of a predictive model. *Arch Phys Med Rehabil*. 1990;71:285-290.
- Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275-282.
- McGinn TG, Guyatt GH, Wyer PC, et al. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. *JAMA*. 2000;284:79-84.
- Koudstaal PJ, Gerritsma JG, van Gijn J. Clinical disagreement on the diagnosis of transient ischemic attack: is the patient or the doctor to blame? *Stroke*. 1989;20:300-301.
- Kraaijeveld CL, van Gijn J, Schouten HJ, et al. Interobserver agreement for the diagnosis of transient ischemic attacks. *Stroke*. 1984;15:723-725.
- Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901-2906.
- Johnston SC, Smith WS. Practice variability in management of transient ischemic attacks. *Eur Neurol*. 1999;42:105-108.
- Cucchiara BL, Messe SR, Taylor RA, et al. Is the ABCD score useful for risk stratification of patients with acute transient ischemic attack? *Stroke*. 2006;37:1710-1714.
- Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369:283-292.
- Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366:29-36.
- Tsivgoulis G, Spengos K, Manta P, et al. Validation of the ABCD score in identifying individuals at high early risk of stroke after a transient ischemic attack: a hospital-based case series study. *Stroke*. 2006;37:2892-2897.
- Bray JE, Coughlan K, Bladin C. Can the ABCD Score be dichotomised to identify high-risk patients with transient ischaemic attack in the emergency department? *Emerg Med J*. 2007;24:92-95.
- Ois A, Gomis M, Rodriguez-Campello A, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. *Stroke*. 2008;39:1717-1721.
- Sciolla R, Melis F. Rapid identification of high-risk transient ischemic attacks: prospective validation of the ABCD score. *Stroke*. 2008;39:297-302.

Critically Appraised Topic (CAT): Review of clinical prediction rules to stratify short-term prognosis of stroke among patients diagnosed in the ED with a transient ischemic attack.

Questions	Are clinical prediction rules (CPRs) useful for predicting which patients have a low (<1%2%) short-term stroke risk after transient ischemic attack?
Reviewed by	Shah K, Metz H, and Edlow J
Date of search	July 2008
Expiration date	July 2010
Clinical bottom line	Although both validated CPRs (California rule and ABCD rule) reasonably predict short-term stroke risk, the ABCD rule has a higher level of evidence because it has been validated in multiple studies. There is increased stroke risk with an increased number of risk factors (higher score). Patients with an ABCD score of <4 are at low risk (<2%) of stroke within 7 days of transient ischemic attack.
Search strategy	The search for studies that reported predictive rules for short-term risk of stroke after transient ischemic attack in PubMed was performed combining the following terms: ("TIA" OR "transient ischemic attack") AND ("stroke" OR "CVA" OR "cerebral vascular accident") and ("score" OR "prediction" OR "prognosis" or "risk"). The same search in EMBASE and DARE was performed using combinations of the following terms: transient ischemic attack, tia, stroke, cerebrovascular accident (cerebrovascular or cerebral vascular accident), cva, score, predict, prognosis, and risk. All 3 searches were limited to the English language, adults (≥19 y), and humans.
Citations	Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. <i>JAMA</i> . 2000;284:2901-2906. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. <i>Lancet</i> . 2005;366:29-36. Tsivgoulis G, Spengos K, Manta P, et al. Validation of the ABCD score in identifying individuals at high early risk of stroke after a transient ischemic attack: a hospital based case series study. <i>Stroke</i> . 2006;37:2892-2897. Bray JE, Coughlan K, Bladin C. Can the ABCD score be dichotomized to identify high-risk patients with transient ischaemic attack in the emergency department? <i>Emerg Med J</i> . 2007;24:92-95. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. <i>Lancet</i> . 2007;369:283-292.
Primary study characteristics	Study Population Johnston et al (2000) followed 1,707 ED patients within the Northern California Kaiser-Permanente system with a primary diagnosis of transient ischemic attack for 90 days. Rothwell et al initially followed 209 adult patients with first-ever transient ischemic attack in the Oxfordshire Community Stroke Project (OCSP) for a 1-mo period. They then followed 190 adult patients with first-ever transient ischemic attack in Oxford Vascular Study (OXVASC) and 210 patients referred to hospital clinics with suspected or probable transient ischemic attack for a 1-mo period. Tsivgoulis et al followed 238 consecutive patients hospitalized with a diagnosis of definite transient ischemic attack for 30 days. Bray et al followed 102 adult ED patients in Melbourne, Australia, with first-ever transient ischemic attack for 90 days. Johnston et al (2007) followed 4,809 combined adult ED and clinic patients with transient ischemic attack in the United States and United Kingdom for 90 days. Outcome Measures Johnston et al (2000) derived the "California rule," a 5-point score. Rothwell et al derived and validated the "ABCD rule," a 6-point score. Tsivgoulis et al and Bray et al validated the ABCD rule. Johnston et al (2007) combined the California and ABCD rules to derive a composite ABCD ² rule, a 7-point score.
Critical appraisal	<i>Level of Evidence (Development of CPR)</i> The ABCD rule has been validated in multiple studies but has not had impact analysis (level 2). The California rule has been validated in only 1 study (level 3). ABCD ² rule has only been derived and validated in a split sample (level 4) and should not be considered ready for clinical use until it has been prospectively validated. <i>Quality Assessment of Individual Studies</i> Rothwell et al applied the ABCD rule to patients presenting to family physicians (but diagnosis confirmed by neurologist) and did not describe the time between symptom onset and presentation to physician. Tsivgoulis et al enrolled only patients admitted to the hospital, which may explain the slightly higher reported stroke risks. Bray et al retrospectively reviewed a small number of patients and did not specify whether the patients had a history of transient ischemic attack. Johnston et al (2007) derived but did not externally validate the composite ABCD ² .

Results

CPR	TIA Study	2-Day Stroke Risk, % (95% CI*)		7-Day Stroke Risk, % (95% CI*)	
		Score <4	Score ≥4	Score <4	Score ≥4
ABCD rule	Rothwell et al	NA	NA	0 (0–1.6)	11.2 (8.1–15.3)
	Tsivgoulis et al	NA	NA	1.7 (0–4.6)	13.2 (8.3–20.2)
	Bray et al	NA	NA	0 (0–11.8)	6.3 (2.1–15.7)
	Johnston et al (2007)	1.3 (0.9–2.0)	5.4 (4.6–6.2)	1.5 (1.0–2.2)	7.7 (6.7–8.7)

*Calculated 95% CI from <http://graphpad.com/quickcalcs/ConfInterval1.cfm>.

Appendix E1. Search strategies.

Database	Search Strategy	Limitations	Total No. of Articles Identified	No. of Articles Reviewed in Detail	No. of Articles Included
PubMed	("TIA" OR "transient ischemic attack") AND ("stroke" OR "CVA" OR "cerebral vascular accident") and ("score" OR "prediction" OR "prognosis" or "risk")	English language, adults (≥ 19 y) and humans	1,811	24	5
EMBASE	1. exp Transient Ischemic Attack/ 2. transient isch?emic attack\$.tw. 3. tia.tw. 4. or/1-3 5. exp STROKE/ 6. stroke\$.tw. 7. Cerebrovascular Accident/ 8. ((cerebrovascular or cerebral vascular) adj accident\$).tw. 9. cva.tw. 10. or/7-9 11. score\$.tw. 12. predict\$.tw. 13. progno\$.tw. 14. risk\$.tw. 15. or/11-14 16. and/4,10,15	English language, adults (≥ 19 y) and humans	919	13	1 (Also selected from PubMed search)
DARE	1. MeSH descriptor Ischemic Attack, Transient explode all trees 2. "transient ischemic attack*":ti,ab 3. "transient ischaemic attack*":ti,ab 4. tia:ti,ab 5. (#1 OR #2 OR #3 OR #4) 6. MeSH descriptor Cerebrovascular Accident explode all trees 7. stroke*:ti,ab 8. (cerebrovascular or cerebral vascular) next accident*):ti,ab 9. cva:ti,ab 10. (#6 OR #7 OR #8 OR #9) 11. (#5 AND #10) 12. score*:ti,ab 13. predict*:ti,ab 14. progno*:ti,ab 15. risk*:ti,ab 16. (#12 OR #13 OR #14 OR #15) 17. (#11 AND #16)	English language, adults (≥ 19 y) and humans	1	0	0

MeSH, medical subject headings.