Critical Review Form
Clinical Prediction or Decision Rule

Clinical prediction rules to stratify short-term risk of stroke among patients diagnosed in the ED with transient ischemic attack, *Ann Emerg Med* 2009; 53: 662-673

Objective: **"To assess existing clinical prediction rules for estimating an individual transient ischemic attack patient's short-term risk for stroke." (p. 663)**

Method: **This short-cut EBM review followed *Annals of Emergency Medicine* Evidence Based Medicine Section methods to essentially conduct a systematic review for one clinical question. The investigators searched 3 data bases (PUBMED,EMBASE,DARE) using the search terms TIA, transient ischemic attack, stroke, cerebrovascular accident and score, prediction, prognosis, or risk in various combinations. In PubMed they applied limits of English language, adults' ≥ 19 years, and human. Two authors independently reviewed 24 articles for inclusion criteria which included: adults > 19 years diagnosed TIA, acute care setting evaluation, stroke outcome within 7 days of TIA, prediction of risk score for such strokes, and derivation or validation studies. Studies evaluating patients presenting weeks after the TIA were excluded.**

Guide		Comments
I.	***Is this a newly derived instrument* (Level IV)?**	

<table>
<tr><td>A.</td><td>Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).</td><td>No. “The ABCD rule has been validated in multiple studies and was assigned a level 2 rating. The ABCD^2 rule has not been validated in other than a split sample and therefore obtains the lowest rating of 4.”(p.670)

Hierarchy of evidence for clinical prediction rules.
<table><tr><th>Level of Evidence</th><th>Application</th><th>Requirements</th></tr><tr><td>Level 1</td><td>Can be used in a wide variety of settings with confidence that they can change clinical behavior and improve patient outcome</td><td>At least 1 prospective validation and 1 impact analysis demonstrating change in clinical behavior with beneficial consequences</td></tr><tr><td>Level 2</td><td>Can be used in various settings with confidence in their accuracy</td><td>Demonstrate accuracy in either 1 large prospective study or validated in several smaller settings</td></tr><tr><td>Level 3</td><td>Clinicians may consider using with caution and only if the patients in the study are similar to those in the clinician’s setting</td><td>Validated in only 1 narrow prospective sample</td></tr><tr><td>Level 4</td><td>Need further evaluation before they can be applied clinically</td><td>Derived but not independently validated</td></tr></table></td></tr>
<tr><td>II.</td><td>Has the instrument been validated? (Level II or III). If so, consider the following:</td><td></td></tr>
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1a	Were all important predictors included in the derivation process? **Yes, see column 5 of Table 4B p 668.**	**California Rule** Age > 60 year (78%) Diabetes (19%) Symptoms _10 min (84%) Unilateral weakness (46%) Speech impairment (52%) **ABCD Rule** **OCSP derivation population** Age > 60 year (12%) HTN (38%) Unilateral weakness (54%) Speech disturbance (13%) Symptom duration > 60 min (36%) 10–59 min (30%) <10 min (33%) **OXVASC validation population** Age > 60 (12.5%) HTN (53%) Unilateral weakness (50%) Speech disturbance (22%) Symptom duration > 60 min (51%) 10–59 min (33%) <10 min (16%) **Hospital clinic validation population** Age > 60 year (12.5%) HTN (52%) Unilateral weakness (38%) Speech disturbance (21%) Symptom duration > 60 min (51%), 10–59 min (29%), < 10 min (21%) **Tsivgoulis Validation** Age > 60 year (61.5%) HTN (56.6%) Unilateral weakness (46.5%) Speech disturbance (42.5%) Symptom duration > 60 min (46.5%) 10–59 min (36.7%) <10 min (16.8%) **Bray Validation** Age > 60 year (79%) HTN (73%) Unilateral weakness (57%) Speech disturbance (19%) Symptom duration > 60 min (79%) 10-59 min (9%) < 10 min (12%) **ABCD^2 Rule** Age > 60 year (77%) HTN (71%) Unilateral weakness (41%) Speech disturbance (19%) Symptom duration > 60 min (62%) 10–59 min (21%) Diabetes (17%)

1b	Were all important predictors present in significant proportion of the study population?	No. Some of the variables in the derivation trials were rare in deriving the California rule the prevalence of various risk factors ranged from 3%-84%. Several risk factors were present in <10% of the cohort including Hispanic, Asian-American, or African-American ethnicity, atrial fibrillation, warfarin use, vertigo, numbness, confusion, gait abnormality, aphasia and dysarthria. The ABCD derivation included far fewer variables with predictor prevalence ranging from 4% to 54%. Only 4% had DM and only 13% had speech disturbance with weakness. (Rothwell 2005, table 1 p.31).
1c	Does the rule make clinical sense?	Yes, the elements of the ABCD, California, and ABCD^2 have face validity for predicting increased risk of cerebrovascular disease as opposed to other causes of TIA-like complaints.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	Only the ABCD rule is Level II clinical decision rule (CDR). "The ABCD rule has been validated in multiple studies and was assigned a level 2 rating. The ABCD^2 rule has not been validated in other than a split sample and therefore obtains the lowest rating of 4." (p.670.) "Johnston et al 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." (and hence Level III CDR) (p. 670).
3	*How well did the validation study meet the following criteria?*	

3a	Did the patients represent a wide spectrum of severity of disease?	Disease severity can be interpreted within the context of TIA-related short-term stroke prognosis in several ways. On the one-hand disease severity may be used to describe the clinical manifestations and duration of TIA presenting symptoms. On the other-hand disease severity could be applied to the stroke-deficit severity and reversibility. In general, this question is meant to focus on the former (pre-outcome spectrum of disease) to ensure that patients are starting from equal or at least adjusted prognostic health status. The current manuscript addresses the former question stratified by eligible study in Table 4B (p. 668) California Rule (Johnson 2000)- 99% of pts presented within 1-day of symptoms, 26% had previous TIA and 23% previous stroke. ABCD (Rothwell 2005)- not described, but all patients with first-ever TIA. (Tsivgoulis 2006)- All cases presenting <48% of symptom onset (88% <24 hours), 35% had TIA in preceding month. (Bray 2007)-median time from symptom onset to ED 135 minutes. ABCD^2 (Johnson 2007)-not well described. **None of the trials described stroke severity or the ability of the CDR's to predict stroke severity.**
3b	Was there a blinded assessment of the gold standard?	The authors assess this for each trial in Table 4B (p. 668) California- Standard criteria for stroke diagnosis independently confirmed by 2 neurologists. ABCD- a) Rothwell 2005-not well described b) Tsivgouliset 2006- well-defined stroke definition c) Bray 2007-retrospective research nurse chart review with good methods ABCD^2- Johnson 2007-retrospective chart review
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Unknown. None of the trials had clinicians interpreting and applying the rules real-time at the bedside. In addition, none of the trials assessed reproducibility (Kappa) for individual elements of the CDR's or for the overall calculated score. In fact, at the end of the article the authors conclude that the patient in the scenario had an ABCD score of 5 based upon her presentation (age > 60, history HTN, unilateral weakness with speech disturbance and symptom duration 10-60 minutes). However, the ABCD rule required a measured ≤ BP >140 or diastolic BP>90 mm Hg to assign 1-point (not a history of HTN). This nicely illustrates the need for explicit descriptors of predictor variables and the value of testing real-time computations/interpretation in the clinical arena.

3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	In the Tsivgouliset study patients discharged from the ED with a diagnosis of TIA were not included (so subsequent strokes were not assessed in presumably lower risk cohort). In the remainder of the studies stroke was sought on all TIA subjects by 1 or 2 Neurologists via chart review.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	

Rule	# Stroke Risks	2-Day % Stroke Risk	7-Day % Stroke Risk
California	0	0 (0-5.4)	0 (0-5.4)
	1	1 (0.4-2.5)	1.2 (0.5-2.8)
	2	1.8 (1.2-2.9)	2.9 (2-4.1)
	3	4.6 (3.5-6.4)	7.5 (6-9.3)
	4	6.8 (4.8-9.5)	10 (7.6-13.1)
	5	7.1 (2.3-17.5)	12.5 (5.9-23.9)
ABCD (Rothwell) OXVASC Population	≤ 1	Not available	0 (0-70)
	2		0 (0-14.3)
	3		0 (0-12.7)
	4		2.2 (0-6.4)
	5		16.3 (6-26.7)
	6		35.5 (18.6-52.3)
ABCD (Tsivgouliset)	0	Not available	0 (0-48.9)
	1		0 (0-28.2)
	2		0 (0-17.6)
	3		1.7 (0-5.1)
	4		7.6 (1.2-14)
	5		19.1 (7.8-30.4)
	6		18.8 (0-37.9)
ABCD (Bray)	0	Not available	0 (0-83.3)
	1		0 (0-44.3)
	2		0 (0-40.4)
	3		0 (0-18.2)
	4		0 (0-23.9)
	5		10.7 (2.9-28)
	6		5 (0-25.4)
ABCD (Johnston)	0	0 (0-9.4)	0 (0-9.4)
	1	1 (0-3.8)	1 (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 (3.9-6.4)
	5	6.1 (4.7-7.8)	8.3 (6.7-10.3)
	6	7.7 (6-9.7)	11.1 (9.1-13.5)
ABCD^2	≤ 1	0 (0-2.2)	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)
	6	8.8 (7-10.9)	12.3 (12.2-14.7)
	7	6.3 (3.3-11.3)	10.6 (6.7-16.4)

		• Among the 4 studies that validated the ABCD score, the risk of stroke was less than 1.7% (range 0-1.7%) at days 2 and 7 if the score was less than 4. • At ABCD scores ≥ 4 the risk of stroke at 2 days was 5.4% and at 7 days ranged from 6.3% to 13.2%. • For the ABCD, California, and ABCD^2 scores, the higher the score the higher the stroke risk.
III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	
1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	"None of the clinical prediction rules have undergone impact analysis and demonstrated change in clinical behavior with beneficial consequences." (p. 670)
2	What was the impact on clinician behavior and patient-important outcomes?	Although level I trials for the TIA prognostic CDR's is currently lacking, "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." (p.671)

Limitations

1) **No attempt to assess publication bias or heterogeneity, although technically this review does not purport to be a systematic review.**

2) **No attempt to objectively quantify the <2% short-term stroke risk. For example, Pauker provided a formula by which to do so even though the conclusion based upon multiple assumptions. The Pauker formula helps to identify a test-and treatment threshold whereby further testing may be detrimental to patients.**

3) **No attempt to explicitly describe how variables are identified as normal or abnormal for each clinical decision rule (see the blood pressure example above in Answer II-3C).**

4) **No description of how to explain this prognostic data to less literate populations.**

5) **Failure to identify that most of these trials were conducted in Caucasian populations and may not produce similar prognostic properties in different ethnic groups.**

Bottom Line

The ABCD rule is the only TIA-prognostic CDR that has been validated in multiple settings and can be reliably applied to heterogeneous populations, but the $ABCD^2$ is very similar and probably will exhibit similar properties when ultimately tested. An ABCD ≤ 3 is associated with a 0% 7-day stroke risk and might be used to identify a subset of TIA patients appropriate for outpatient work-up. Future trials are needed to:

a) **Validate the $ABCD^2$, particularly in non-Caucasian populations;**
b) **Assess the reliability and accuracy of the ABCD or $ABCD^2$ when used prospectively at the bedside by busy EM clinicians;**
c) **Assess the impact of ABCD/$ABCD^2$ use on resource utilization and patient-centric outcomes.**