Critical Review Form
Clinical Prediction or Decision Rule

Validation and refinement of scores to predict very early stroke risk after Transient Ischaemic Attach, *Lancet* 2007; 369:283-292

Objectives:

1) **"To validate the two existing prognostic scores in large independently assembled groups from different populations, comparing predictions of stroke risk at 2-, 7-, and 90-days".**
2) **"To generate a new unified score that would improve prediction of risk of stroke in the 2-days after TIA".**
3) **Then validate the new score. (p.283)**

Methods: Investigators who had independently already developed two TIA prognostic screening tools (ABCD score and California score) used their derivation cohorts to validate one another's previous rule. The four randomly selected validation cohorts included:

1) **Patients diagnosed with TIA in one of 16 California ED's;**
2) **Kaiser-Permanente outpatient clinics;**
3) **Population based sampling of 63 Oxford (England) family practice clinics;**
4) **Oxford patients referred to a hospital-based TIA clinic.**

While the California cohort had variables and diagnoses based upon chart review, the British patient information was obtained by face-to-face neurologist follow-up at 1-, 6-, 12- and 24-months. For all groups, the initial diagnosis of TIA was based entirely upon the opinion of the initial treating doctor. Timing of events during follow-up was from the point of patient presentation not TIA symptom onset.

First the investigators validated the two existing scores (ABCD and California) on all groups except those in who they had been derived with prognostic performance judged by c-statistic (AUC). Next, each element of the ABCD and California score was analyzed as a predictor of 2-day stroke risk (Table 5, p.289). Various combinations of the individual elements were tested until that with the maximal c-statistic for 2-day stroke risk was attained. The new tool ($ABCD^2$) was then tested on each of the validation cohorts.

Guide		Comments
I.	***Is this a newly derived instrument* (Level IV)?**	
A.	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).	No – a new data base of subjects was used to validate the ABCD and California rules so those are now Level III. The $ABCD^2$ is still a Level IV since it was validated on only one retrospective cohort.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	Yes – the original derivation trials included all important prognostic predictors.
1b	Were all important predictors present in significant proportion of the study population?	Yes. Table 1 (p.285) demonstrates that the least prevalent predictor (duration <60-minutes) was present in 16-32% of cohorts.
1c	Does the rule make clinical sense?	Yes, the rule makes sense. With the $ABCD^2$ mnemonic it is easy to remember and each element has content validity.
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)?	The ABCD and California rules are Level II having been derived and validated in ED's outpatient, inpatient, and specialty clinic populations. The $ABCD^2$ rule is technically a Level IV rule given its retrospective validation. However, given the wide-range of populations included and the close approximation of ABCD to $ABCD^2$, the latter CDR is realistically a Level III and common sense dictates it could be applied to ED populations similar to those in California.
3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Yes. Table 1 (p.285) illustrates an impressive heterogeneity of prognostic baseline risk.
3b	Was there a blinded assessment of the gold standard?	In California, Neurology chart review was the Gold standard. Neurologists were likely unaware of the CDR being developed, but this isn't explicitly stated.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Probably, since the variables were retrospectively obtained (i.e., recorded before the rule was derived in California). Similarly in England the data was recorded before derivation of the ABCD.

3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	No, all subjects had the same (albeit different between UK & US) Gold standard applied in England and California.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	<u>California score</u> • A score of 0 was associated with a 0% 7-day stroke rate and only 0.06% (2/3084) 90-day stroke rate in all validation groups • C-statistic varied 0.61 – 0.74. <u>ABCD score</u> • A score of 0 was associated with 0% 90-day stroke rate in all validation groups, while a score of 1 had a 2 – 5% stroke rate at 90 days. • Among ED cohorts an ABCD ≤ 1 had a 0% 2-day stroke risk. • C-statistic varied 0.62 – 0.81. <u>ABCD^2 score</u> • A score of 0 was associated with a 0% 90-day stroke rate in all cohorts, while a score of 1 had a 1 – 3% 90-day stroke rate. However, less than 1% of the cohort had a score of 0 (and 5% had a score ≤ 1. • The 2-day stroke risk for ABCD^2 ≤ 1 was 0%, but for a score of 2 the 2-day stroke risk was 1 – 2%. The authors advocate for an ABCD^2 ≤ 3 as "low risk" although ED-cohorts had a 2 – 3% 2-day stroke risk with scores of 3. • C-statistic varied from 0.66 – 0.83, widely overlapping with the ABCD and California prognostic performance.

		• LR's calculated from Table 4. **ABCD²** / **LR+** / **LR-** 0 / 1 (1-1.02) / 0 (0.02-4) ≤ 1 / 1.05 / 0 (0-0.8) ≤ 2 / 1.16 / 0.22(0.1-0.5) ≤ 3 / 1.41 / 0.26(0.2-0.4)

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)?	No formal impact analysis was conducted.
2	What was the impact on clinician behavior and patient-important outcomes?	No formal impact analysis was conducted, but 15% of strokes occurred in patients not admitted to the hospital and 41% on $ABCD^2$ score > 5 so a policy dictating admission for only high-risk patients (which is not the intent of any CDR) would have resulted in hospital admission for 23% (compared with the baseline rate of 9.1%) and 48% of strokes would have occurred in those admitted. If all $ABCD^2$ > 3 were admitted, 66% admission rates would occur and 91% of strokes occurring would have been in those admitted.

Limitations

1) **Events were counted from presentation to a physician rather than from symptom onset so some early strokes may have been missed. However, this more realistically approximates clinical practice.**
2) **The authors discuss stroke rates, but not the patient – important outcome of stroke prevention. If admission to the hospital only means the stroke occurs in the hospital rather than at home, who cares? Does admission for higher risk stroke patients for expedited work-up diminish stroke risk or improve post-stroke outcomes?**
3) **Retrospective validation of the $ABCD^2$ rule risks over-fitting. To assure similar results in distinct populations, separate prospective validation trials are required.**
4) **Some California data were gathered retrospectively. Whether clinicians would collect and interject the variables of $ABCD^2$ when gathered prospectively remains uncertain.**

Bottom Line:

In assessing 2-day post-TIA stroke risk, the California rule, ABCD, and $ABCD^2$ display similar prognostic capabilities. The $ABCD^2$ prognostic guide may be slightly superior. To minimize post-TIA stroke risk among ED patients a score of ≤ 1 was associated with a 0% 2-day risk on the validation cohorts. $ABCD^2$ score of ≤ 3 has a 1% 2-day stroke risk while a score of > 5 has an 8% risk. Before widespread adoption of the $ABCD^2$ rule future research should validate the prognostic test characteristics prospectively on distinct populations. Furthermore, clinicians will need to be convinced that admission of high-risk TIA patients improves outcomes.

ABCD^2 Rule

Risk Factor	Points
Age > 60 years	1
Initial BP > 140/90	1
Unilateral weakness	2
Speech Impairment without weakness	1
Symptom Duration 10-59 minutes	1
Symptom Duration > 60 minutes	2
History of Diabetes	1

Score	Risk Category	2-Day Stroke Risk	7-Day Stroke Risk
≤ 3	Low	1%	1.2%
4-5	Moderate	4.1%	5.9%
>5	High	8.1%	11.7%