Validation and comparison of imaging-based scores for prediction of early stroke risk after transient ischaemic attack: a pooled analysis of individual-patient data from cohort studies

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Summary

Background

Identification of patients at highest risk of early stroke after transient ischaemic attack has been improved with imaging based scores. We aimed to compare the validity and prognostic utility of imaging-based stroke risk scores in patients after transient ischaemic attack.

Methods

We did a pooled analysis of published and unpublished individual-patient data from 16 cohort studies of transient ischaemic attack done in Asia, Europe, and the USA, with early brain and vascular imaging and follow up. All patients were assessed by stroke specialists in hospital settings as inpatients, in emergency departments, or in transient ischaemic attack clinics. Inclusion criteria were stroke-specialist confirmed transient ischaemic attack, age of 18 years or older, and MRI done within 7 days of index transient ischaemic attack and before stroke recurrence. Multivariable logistic regression was done to analyse the predictive utility of abnormal diffusion-weighted MRI, carotid stenosis, and transient ischaemic attack within 1 week of index transient ischaemic attack (dual transient ischaemic attack) after adjusting for ABCD2 score. We compared the prognostic utility of the ABCD2, ABCD2-I, and ABCD3-I scores using discrimination, calibration, and risk reclassification.

Findings

In 2176 patients from 16 cohort studies done between 2005 and 2015, after adjusting for ABCD2 score, positive diffusion-weighted imaging (odds ratio [OR] 3·8, 95% CI 2·1–7·0), dual transient ischaemic attack (OR 3·3, 95% CI 1·8–5·8), and ipsilateral carotid stenosis (OR 4·7, 95% CI 2·6–8·6) were associated with 7 day stroke after index transient ischaemic attack ($p<0·001$ for all). 7 day stroke risk increased with increasing ABCD2-I and ABCD3-I scores (both $p<0·001$). Discrimination to identify early stroke risk was improved for ABCD2-I versus ABCD2 (2 day c statistic 0·74 vs 0·64; $p=0·006$). However, discrimination was further improved by ABCD3-I compared with ABCD2 (2 day c statistic 0·84 vs 0·64; $p<0·001$) and ABCD2-I (c statistic 0·84 vs 0·74; $p<0·001$). Early stroke risk reclassification was improved by ABCD3-I compared with ABCD2-I score (clinical net reclassification improvement 33% at 2 days).

Interpretation

Although ABCD2-I and ABCD3-I showed validity, the ABCD3-I score reliably identified highest-risk patients at highest risk of a stroke after transient ischaemic attack with improved risk prediction compared with ABCD2-I. Transient ischaemic attack management guided by ABCD3-I with immediate stroke-specialist assessment, urgent MRI, and vascular imaging should now be considered, with monitoring of safety and cost-effectiveness.

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Research in context

Evidence before this study

We searched PubMed and MEDLINE between Jan 1, 2010, and June 26, 2016, with the terms "ABCD2 and ABCD3-I and transient ischaemic attack" or and "ABCD2-I and ABCD3-I and transient ischemic attack". We also searched the reference lists of identified articles and our own files. We included peer-reviewed articles published in English that compared the performance of the ABCD3-I score for stroke prediction with other transient ischaemic attack risk prediction scores. We found four publications that met our inclusion criteria, all of which compared discrimination of the ABCD3-I score with the ABCD2 score, and one of the four compared the ABCD3-I score with the ABCD2-I score.

Added value of this study

Using recommended metrics for evaluation of prognostic models and scores, this study validates the ABCD3-I prediction score for identification of patients at highest early stroke risk after transient ischaemic attack when used by stroke specialists in acute hospital settings (after admission, in emergency departments, or in transient ischaemic attack clinics). Our findings show the improved predictive performance of the ABCD3-I score compared with the ABCD2 and ABCD2-I scores.

Implications of all the available evidence

Our findings lend support to the wider use of the ABCD3-I score for risk stratification of patients with transient ischaemic attack in acute hospital settings. It provides a rationale for reorganising services by providing early access to brain MRI and vascular imaging at the point of initial assessment of transient ischaemic attack. Our data suggest that, if carefully applied and monitored, algorithms based on the ABCD3-I score can be used to select patients at high stroke risk for admission to hospital for acute treatment.

Introduction

Transient ischaemic attack is associated with high risk of early subsequent stroke in 10–20% of patients.[1] This risk is not uniform, and depends on the patient's clinical characteristics, underlying pathophysiology of transient ischaemic attack, and early treatment. Accurate identification of patients at highest risk of stroke after transient ischaemic attack is essential to target acute treatment safely and effectively, and to prevent early recurrent stroke.

Following earlier descriptions of clinical variables that were associated with increased stroke risk after transient ischaemic attack, the ABCD2 prediction score (range 0–7, age, blood pressure, clinical symptoms, duration, and diabetes) was derived to improve risk stratification of patients with transient neurological symptoms.[2–4]

Although externally validated in earlier studies, the ABCD2 score was originally intended to aid clinical management of patients assessed by non-specialists in community and emergency department settings, and has little specificity when used by hospital-based stroke specialists.[5–7]

To guide risk-based treatment decisions after stroke-specialist assessment, the ABCD2 score has been extended to include imaging findings in the ABCD2-I (range 0–10, addition of brain imaging only) and ABCD3-I scores (range 0–13, addition of recent earlier dual transient ischaemic attack defined as the index transient ischaemic attack and at least one other transient ischaemic attack in the 7 days before index event, carotid imaging, and

brain imaging).[8,9] The discrimination of patients with high-risk transient ischaemic attack was improved with both imaging-based scores compared with the ABCD2 score in the original derivation cohorts,[8,9] lending support to their potential to improve the accuracy of early stroke risk prediction. However, several issues remain to be clarified before the scores can be judged suitable for wider use. First, few validation studies of imaging-based scores have been done, with limitations such as small sample sizes and inclusion of patients imaged with brain CT, which has lower sensitivity than MRI for detection of minor ischaemic change after transient ischaemic attack symptoms.[9–15] Second, whether the inclusion of information about previous transient ischaemic attack and vascular imaging in the ABCD3-I score provides additional prognostic value to the inclusion of brain imaging alone in the ABCD2-I and other similar risk models is unclear.16–18

In this study, we aimed to analyse the external validity and directly compare the predictive utility of imaging-based stroke risk scores after transient ischaemic attack in a pooled sample of individual patients from international cohort studies.

Methods

Search strategy and selection criteria

AM did a literature search to identify potentially eligible patient samples for inclusion in the pooled individual-patient data (IPD) analysis. AM searched PubMed, AMED, BNI, CINAHL, Embase, Health Business Elite, HMIC, MEDLINE, PsycINFO, Google Scholar, and Scopus up to Nov 14, 2015, with the search terms "ABCD2*" or "ABCD3*", and "TIA", and "transient ischaemic attack", for studies published since the 2010 ABCD3-I publication on Oct 8, 2010.[9] Conflicts over inclusion were resolved after discussion between two authors (AM and PJK). We also searched the reference lists of the identified articles, and searched Google Scholar, Scopus, and our own files. We included articles published in English or with abstracts in English. Additionally, we hand searched abstracts from recent international stroke conferences. Studies were assessed for methodological quality in terms of study design, stroke after transient ischaemic attack as main outcome, and availability of brain imaging data. Our search revealed 19 publications describing potentially eligible samples. Of these, 12 groups were contacted and agreed to participate, five declined to participate in IPD analysis, and two could not be contacted. Five groups in Toulouse (France), Stanford (CA, USA), Athens (Greece), and Dublin and Oxford (UK) provided additional unpublished data (appendix pp 5, 6).

Study design and participants

We did a pooled analysis of individual-patient data from 16 cohort studies that had been done by 12 collaborative groups at 16 centres in Asia, Europe, and the USA, all reporting independent validation cohorts that were not used in the original derivation of the ABCD3-I score.

Predefined inclusion criteria for patients were: transient ischaemic attack confirmed by a stroke specialist, age of 18 years or older, and brain MRI information available within 7 days of transient ischaemic attack onset and before stroke recurrence. Patients were excluded if a diagnosis other than transient ischaemic attack was made, they first sought medical attention, or had brain imaging for a stroke recurrence rather than the index transient ischaemic attack. All patients were assessed in hospital settings by stroke specialists, either as inpatients, in emergency departments, or in transient ischaemic attack clinics.

Standard definitions of all variables were provided to all centres before data abstraction using a data dictionary. Data were abstracted from existing transient ischaemic attack registries at each centre using a standardised electronic template, locally de-identified, and collated centrally. Teleconferences were arranged with participating centres to discuss data definitions if necessary. All data (published and unpublished) were combined in a central database and coded with a centre identifier number or code. Decisions relating to early treatment and hospital admission at each centre were at the discretion of the treating clinician in this study. The cohorts included in this were not included in the original derivation sample for the ABCD3-I score.

For comparison of our findings with the original ABCD2-I and ABCD3-I derivation samples and external validation studies, we used the WHO clinical definition of transient ischaemic attack: an acute loss of focal

cerebral or ocular function lasting less than 24 h, without an apparent non-vascular cause.[19] The prognostic utility of the imaging-based scores was assessed in tissue-defined transient ischaemic attack (ie, absence of ischaemic injury on diffusion-weighted imaging) as proposed by the American Stroke Association in a pre-specified secondary analysis.[20]

The index transient ischaemic attack for study inclusion was defined as that most recently preceding stroke-specialist assessment. Dual transient ischaemic attack was defined as the occurrence of at least two transient ischaemic attacks: the index transient ischaemic attack, and at least one other transient ischaemic attack in the 7 days before the index event. For standardisation and generalisability, we used the WHO definition of stroke—ie, a new neurological deficit that occurred after complete resolution of symptoms of the preceding transient ischaemic attack.[19]

Atrial fibrillation was defined as pre-existing or newly detected atrial fibrillation on electrocardiogram or continuous cardiac rhythm monitoring after transient ischaemic attack. Carotid stenosis was defined as a 50% or more narrowing of the ipsilateral internal carotid artery lumen on carotid imaging (including duplex ultrasound, CT, or magnetic resonance angiogram, or angiography), as interpreted by the reporting physician at each centre using the NASCET method.[21]

Diffusion-weighted MRI hyperintensity was defined as lesions consistent with acute cerebral ischaemia as judged by the treating physician at each centre. Diffusion-weighted MRI artifact caused by gliosis or Virchow-Robin spaces (T2 shine through) must have been judged unlikely, using apparent diffusion coefficient (ADC) images or other supporting data. MRIs were done on 1·5 or 3 Tesla scanners within 7 days of index transient ischaemic attack onset.

Recurrent stroke within 2 days, 7 days, 28 days, and 90 days after index transient ischaemic attack was assessed in person, or by telephone interview and medical file review. Data from patients with peri-procedural stroke following carotid revascularisation (endartectomy or stenting) were excluded from analysis and not sought from participating centres.

Local ethics committee and institutional review board approval was obtained at each centre for each study in accordance with local regulations. Patients included in the study provided informed consent (written or verbal) for use of their data for research into stroke prevention following transient ischaemic attack.

Statistical analysis

Statistical analysis was done with R (version 3.1.3) and Stata (version 12). Parametric and non-parametric comparisons of categorical and continuous variables were done with χ^2, *t* test, and Mann-Whitney *U* test, as appropriate. All significance tests were two-sided. A p value of 0·05 or less was deemed significant. We used bivariate logistic regression to assess the association of vascular risk factors and variables included in the ABCD2 score with 7 day stroke (ie, stroke within 7 days). Multivariable logistic regression analysis of the additional prognostic utility of positive diffusion-weighted MRI, carotid stenosis, and dual transient ischaemic attack to the ABCD2 score (ie, parameters included in the ABCD2-I and ABCD3-I scores) was done with 7 day stroke as the dependent variable. For multivariable analysis of the relation between dual transient ischaemic attack, diffusion-weighted MRI, and carotid stenosis with early stroke risk, the ABCD2 score was included in each model as a continuous variable. Clinical variables included in the ABCD2 score were analysed individually using bivariate logistic regression. The ABCD2-I and ABCD3-I scores were analysed as ordinal variables and classified into low, medium, and high categories (0–3, 4–7, and 8–10 for ABCD2-I, and 0–3, 4–7, and 8–13 for ABCD3-I).

Missing data were addressed with a prespecified standardised three-step approach. First, investigators were requested to re-check source datasets for potential data point misclassifications. Second, if deemed valid based on other available variables, values for missing variables were imputed from the supplied clinical data (eg, if MRI done variable missing, but diffusion-weighted MRI positive variable coded, then MRI done was imputed

as yes). Third, if clinically valid assumptions could not be made for an essential data variable (eg, follow-up stroke status), the case was excluded from the primary analysis.

Direct comparisons of imaging-based scores were done using the subset of patients for which all relevant variables for each score and early follow-up stroke status were available. We directly compared discrimination of the ABCD2, ABCD2-I, and ABCD3-I scores using receiver-operating characteristic analysis and the *c* statistic (area under curve) calculated at 2 days and 7 days after the index transient ischaemic attack.[21] Ideal discrimination produces a *c* statistic of 1·0, whereas discrimination that is no better than chance produces a *c* statistic of 0·5. 95% CIs and related p values for comparison of *c* statistics were obtained from bootstrap replicates, accounting for the inter-relatedness of variables included in each prognostic score.

Calibration of the ABCD2-I and ABCD3-I scores was assessed by comparing the approximation of predicted risk from the original derivation papers for each score, with observed risk in the validation sample.[22] For each score level, the predicted number of events in the validation sample was calculated based on the risk observed in the original derivation cohorts, and compared with observed risk in the validation sample. Predicted and observed risks were then compared using the χ^2 for each comparison. χ^2 greater than 20 was interpreted as indicating poor approximation of observed with predicted risk and thus reduced calibration, according to criteria recommended by D'Agostino.[23] Because of the low rate of events or no events at the extremes of each score (eg, no events were observed at ABCD3-I scores of 0 or 1), the score strata were classified into groups containing sufficient events for calculation of the χ^2 statistic (with 6 degrees of freedom for ABCD2-I and 5 degrees of freedom for ABCD3-I χ^2 statistic).

Risk reclassification from ABCD2 to ABCD2-I and ABCD3-I scores was assessed with cross tabulation. The net improvement in reclassification across clinically relevant risk categories (clinical net reclassification improvement [CNRI]) was calculated and compared for each score. Risk reclassification grids were constructed to illustrate the net changes in risk assignment from ABCD2 or ABCD2-I score to ABCD3-I score, stratified by the subsequent occurrence or non-occurrence of stroke events (ie, appropriate or inappropriate risk reclassification up or down score risk categories). Non-categorical risk reclassification across the entire spectrum of the scores (net reclassification improvement) was also calculated (appendix p 9).[24–26] Because of concerns about the validity of hypothesis tests for comparison of risk reclassification by prognostic models, no p values are reported.[26] When adding NRI values for events (strokes) and non-events to produce a summary overall value, an underlying assumption is that the consequence of misclassifying a high-risk patient as low is equivalent to that of misclassifying a low-risk patient as high risk. Therefore, NRI values are reported separately for events and nonevents, and combined.

We did prespecified sensitivity analyses to assess the prognostic utility of the scores in patients with American Stroke Association tissue-defined transient ischaemic attack (absence of ischaemic injury on diffusion-weighted MRI), patients with clinical transient ischaemic attack but positive diffusion-weighted MRI (transient symptoms with infarction), Asian, and non-Asian subgroups, and in those imaged with brain CT but not MRI.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

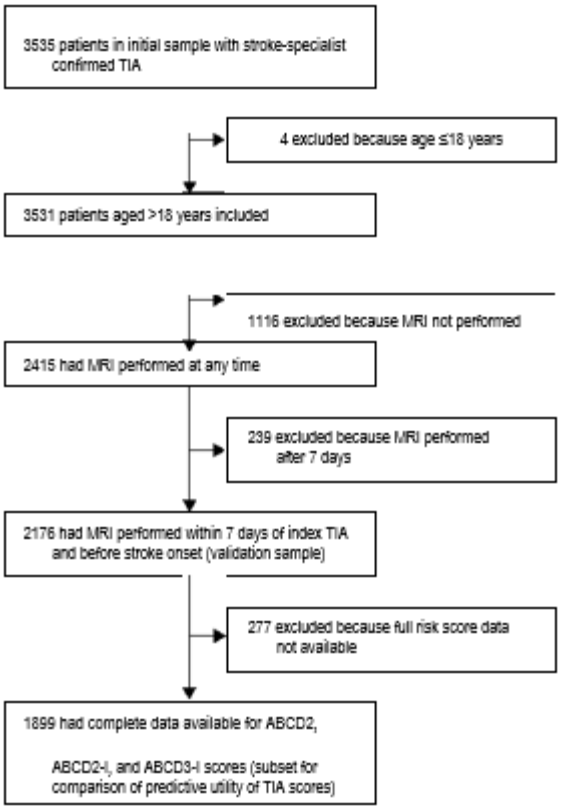

Figure 1: **Study profile**
TIA=transient ischaemic attack.

Results

Between 2005 and 2015, 16 centres in Europe, the USA, and Asia (listed in appendix p 5, 6) contributed individual-patient data from 3535 patients with transient ischaemic attack. Of these, 2176 patients met prespecified eligibility criteria (ie, transient ischaemic attack confirmed by a stroke specialist, age >18 years, and MRI done within 7 days of transient ischaemic attack onset) and were included in the pooled analysis (figure 1). Table 1 and the appendix (p 5, 6) show the clinical characteristics of the patients included and excluded from the study. Complete data were available for ABCD2 score calculation in 2153 (99%) of 2176 patients, diffusion-weighted MRI for transient ischaemic attack evaluation in 2161 (99%) patients, carotid imaging in 2082 (96%) patients, dual transient ischaemic attack in 1980 (91%) patients, and 7 day stroke occurrence in 2108 (97%) patients. The median age of included patients was 68 years, 59% were men, 19% were current smokers, and 13% had atrial fibrillation (table 1). Diffusion-weighted MRI hyper-intensity after index transient ischaemic attack was present in 31% (681 of 2176 patients), and carotid stenosis in 12% (table 1).

Stroke after index transient ischaemic attack occurred in 30 (1%) of 2085 patients at 2 days and 49 (2%) of 2108 patients at 7 days (table 1). When clinical variables included in the ABCD2 score were analysed individually only motor or speech symptoms were associated with increased 7 day stroke risk (OR 3·3, 95% CI 1·9–5·9; p<0·001). However, when analysed as an ordinal variable, higher ABCD2 score was associated with greater risk of 7 day stroke (OR per 1-point increase in score 1·4, 95% CI 1·1–1·7, p=0·004 for trend). Smoking, atrial fibrillation, and acute medication use before or after index transient ischaemic attack were not associated with early increased stroke risk. Ischaemic injury on diffusion-weighted MRI for evaluation of the index transient ischaemic attack (OR 4·3, 95% CI 2·4–7·7), dual transient ischaemic attack within 7 days of index transient ischaemic attack (3·0, 1·7–5·4), and ipsilateral carotid stenosis (5·1, 2·8–9·2) were associated with increased

stroke risk at 7 days and other early timepoints (28 and 90 days; appendix p 7). On multivariable logistic regression, after adjusting for ABCD2 score, positive diffusion-weighted MRI remained as an independent predictor of increased 7 day stroke (OR 3·8, 95% CI 2·1–7·0). When brain imaging was incorporated with ABCD2 as the ABCD2-I score, the risk of having a stroke within 7 days of transient ischaemic attack increased with increasing ABCD2-I score ($p<0·001$ for linear trend). When ABCD2-I was classified into low (0–3), medium (4–7), and high (8–10) categories, 7 day stroke rates were higher with higher risk categories ($p<0·001$ for trend; figure 2A). For stroke risk stratified by ABCD2-I categories, at 2 days, stroke risk was 0·19% (1/516 patients, ABCD2-I 0–3), 1·92% (20/1039 patients, ABCD2-I 4–7), and 3·45% (9/261 patients, ABCD2-I 8–10). Corresponding risks at 7 days were 0·58% (3/516 patients), 2·85% (30/1054 patients), and 5·66% (15/265 patients; figure 2A).

After adjusting for ABCD2 score, both dual transient ischaemic attack (OR 3·3, 95% CI 1·8–5·8) and carotid stenosis (4·7, 2·6–8·6) were independent predictors of increased risk of 7 day stroke. After further adjustment for ABCD2 score and positive diffusion-weighted MRI (ie, items included in the ABCD2-I score), dual transient ischaemic attack (OR 3·0, 95% CI 1·6–7·4), and carotid stenosis (OR 4·1, 95% CI 2·2–7·5) remained as independent predictors of increased early stroke risk. When these variables were included together as the ABCD3-I score, 7 day stroke risk increased linearly with increasing ABCD3-I score ($p<0·001$ for trend). When patients were classified by ABCD3-I score as low (0–3), medium (4–7), and high (8–13) categories, stroke risk increased with increasing score category ($p<0·001$ for trend; figure 2B). Of the patients with an ABCD3-I score of 0 or 1, none had stroke at 7 days (0 of 58 patients) compared with 17% (one of six patients) with a score of 12 (no patient had a maximum score of 13). When stratified by ABCD3-I category, stroke risk at 2 days was 0·25% (1/407 patients, ABCD3-I 0–3), 0·72% (8/1108 patients, ABCD3-I 4–7), and 6·98% (21/301 patients, ABCD3-I 8–13). Corresponding risks at 7 days were 0·49% (2/408 patients), 1·60% (18/1126 patients), and 9·3% (28/301 patients; figure 2B).

For direct comparison of ABCD2, ABCD2-I, and ABCD3-I scores, data were complete for all exposure variables in 1899 patients, with complete data for stroke outcome at 2 days and 7 days in 1816 of these patients. 30 (2%) of these patients had stroke at 2 days and 48 (3%) at 7 days. The ABCD2-I score was better than the ABCD2 score for discrimination of patients with transient ischaemic attack who had stroke at 2 days (*c* statistic 0·74 *vs* 0·64, $p=0·006$). However, the ABCD3-I score was better than the ABCD2 score for the discrimination of 2 day stroke (0·84 *vs* 0·64; $p<0·001$) and the ABCD2-I score (0·84 *vs* 0·74; $p<0·001$; figure 3). Figure 3 shows area under the curves for each score for stroke within 2 and 7 days of transient ischaemic attack. These findings were consistent when the analysis was repeated for risk of stroke at 7 days (figure 3), 28 days, and 90 days (table 2).

Across the entire range of each score, risk reclassification was improved for each imaging-based score compared with the ABCD2 score. For risk of stroke at 2 days, the net reclassification improvement for the ABCD2-I score was 36% and for the ABCD3-I score was 41% (appendix p 9). However, for score categories used for clinical decision making (CNRI), risk reclassification was improved for the ABCD3-I score (CNRI 34%) but only slightly for the ABCD2-I score (CNRI 12%) compared with ABCD2 (appendix p 8). Risk reclassification was further improved by the ABCD3-I score compared with the ABCD2-I score. For stroke at 2 days, the net reclassification improvement was 69% (appendix p 9) and the CNRI was 33%. Findings were similar for risk of stroke at 7 days (appendix pp 8, 9).

On visual inspection of reclassification grids (figure 4), at each time interval, a substantially greater proportion of patients who subsequently had a stroke (event) were correctly reassigned as higher risk by the ABCD3-I score, at a smaller cost of inappropriately reassigning a smaller proportion of patients who did not have an event. We compared the observed stroke risk at 7 days for each ABCD3-I score category in the pooled validation cohort for which all score exposure data were available (1899 patients) with expected risk based on the original derivation cohort (2654 patients, 55% men, mean age 65·4 years).[9] The observed stroke risk closely approximated expected risk (appendix pp 11, 12). χ^2 was 17·9 (5 degrees of freedom).[23] By contrast, approximation of observed risk with expected risk for the ABCD2-I score was poor, with overestimation of

observed risk at most levels of the score. χ^2 was 93·9 (6 degrees of freedom), indicating poor calibration[23] (appendix pp 11, 12).

To explore the potential application of a single ABCD3-I risk threshold in clinical practice, we assessed the distributions of patients who had a stroke within 7 days of transient ischaemic attack (48 patients) and proportions of the cohort for which ABCD3-I score and stroke outcome were complete (1835 patients) when the ABCD3-I score was dichotomised as 0–7 and 8–13. Although 84% (1534 of 1835 patients) of the cohort had ABCD3-I scores of 0–7, the 7 day stroke risk in this group was 1·3% (n=20, 95% CI 0·73–1·87). By contrast, in the 16% (n=301) of the cohort with ABCD3-I scores of 8 or greater, 7 day stroke risk was 9·3% (n=28, 95% CI 6·0–12·6). Of the 48 patients who had a stroke within 7 days, 28 (58%) were in the high-risk subgroup (ABCD3-I ≥8), whereas 42% (20 patients) of stroke outcomes occurred within the much larger group with ABCD3-I lower than 8 (1534 patients).

When dichotomised, the specificity of an ABCD3-I score of 8 or higher for identification of patients with transient ischaemic attack who had subsequent stroke by 7 days was 85%, with sensitivity of 58%. The positive predictive value (probability of 7 day stroke in patients with ABCD3-I ≥8) was 9·3%, while the negative predictive value (probability that 7 day stroke will not occur in patients with ABCD3-I 0–7) was 98·7%.

For patients with tissue-defined transient ischaemic attack without ischaemic injury on diffusion-weighted MRI (by definition diffusion-weighted MRI negative), the brain imaging item was scored 0 and ABCD2-I was equal to ABCD2 score. In this subgroup (1495 patients), discrimination with the ABCD3-I score was greater than with ABCD2 and ABCD2-I for stroke at all early timepoints (appendix p 10). In the subgroup with clinical transient ischaemic attack but positive diffusion-weighted MRI (ie, transient symptoms with infarction, 681 patients), the ABCD3-I score also showed improved discrimination at 2 days (*c* statistic 0·76, 95% CI 0·66–0·85 *vs* 0·53, 0·42–0·62; p<0·001) and 7 days (*c* statistic 0·70, 95% CI 0·60–0·79 *vs* 0·55, 0·46–0·63; p<0·001) compared with ABCD2.

Discrimination for stroke at 2 days and 7 days was also greater with ABCD3-I than with ABCD2 and ABCD2-I scores in non-Asian cohorts, but the difference in *c* statistics was attenuated in the Asian subgroup and not significant, possibly related to low statistical power (25 strokes at 7 days in 381 Asian patients; data not shown). No predictive score had discrimination better than chance in the subgroup of the original cohort imaged by CT only (42 strokes in 504 patients at 7 days; data not shown).

	Patients included* (n=2176)		Patients excluded*		p value (n=1359)
Men	1274/2174	(59%)	714/1347	(53%)	0·004
Age (years)	68 (57–77)		69 (59–78)		0·01
Hypertension	1459/2146	(68%)	890/1342	(66%)	0·3
Hyperlipidaemia	708/1737	(41%)	612/1240	(49%)	<0·001
Atrial fi brillation	272/2141	(13%)	204/1104	(18%)	<0·001
Dual transient ischaemic attack	414/1980	(21%)	136/1114	(12%)	<0·001
Current smoker	412/2140	(19%)	288/1190	(24%)	0·001
Coronary artery disease	270/1873	(14%)	238/1271	(19%)	<0·001
Carotid stenosis	249/2082	(12%)	207/1303	(16%)	0·001
Diabetes	361/2171	(17%)	253/1354	(19%)	0·1
Post transient ischaemic attack statin	1134/1560	(73%)	717/932	(77%)	0·02
Post transient ischaemic attack antiplatelet	1290/1594	(81%)	784/940	(83%)	0·1
MRI done	2176/2176	(100%)	250/782	(32%)	<0·001
ABCD2 score	4 (3–5)		4 (3–5)		0·4
Stroke recurrence					
2 days	30/2085	(1%)	46/1326	(3%)	<0·001
7 days	49/2108	(2%)	83/1327	(6%)	<0·001
28 days	61/2068	(3%)	99/1305	(8%)	<0·001
90 days	80/2051	(4%)	132/1260	(10%) <0·001	<0·001

Data are n/N (%) or median (IQR). *Not all data items were available for all variables.

Table 1: Clinical characteristics of patients included in our pooled analysis compared with excluded patients

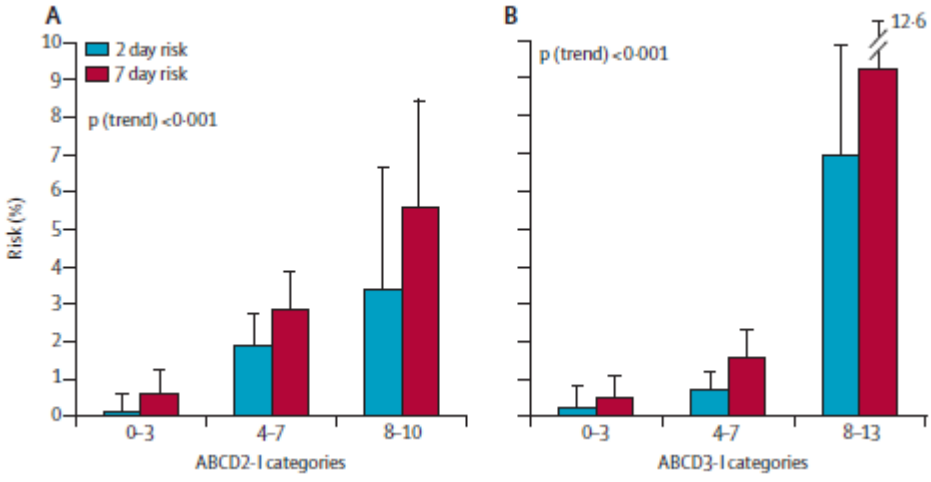

Figure 2: **Stroke risk after transient ischaemic attack stratifi ed by ABCD2-I and ABCD3-I categories**
(A) Stroke risk stratifi ed by ABCD2-I categories at 2 days and 7 days. (B) Stroke risk stratifi ed by ABCD3-I categories. Error bars indicate 95% CIs.

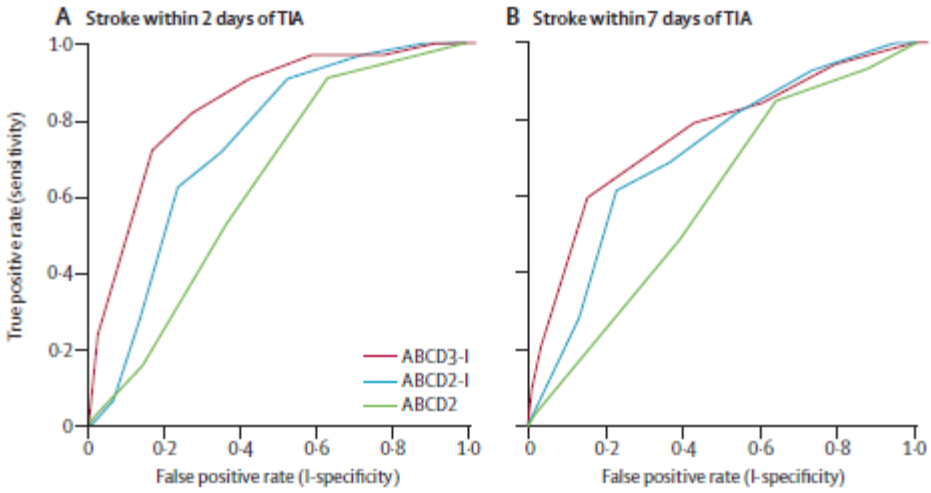

Figure 3: **Area under receiver-operating characteristic curves for discrimination of patients with TIA with subsequent stroke by ABCD2, ABCD2-I, and ABCD3-I scores**
(A) Area under the curve for each score for stroke within 2 days of TIA. (B) Area under the curve for each score for stroke within 7 days of TIA. TIA=transient ischaemic attack.

	ABCD2		ABCD2-I		p value (ABCD2 *vs* ABCD2)-1	ABCD3-I		p value (ABCD2 *vs* ABCD3-I)	p value (ABCD2-I *vs* ABCD3-I)
Day 2 stroke	0·64	(0·56–0·71)	0·74	(0·67–0·80)	0·006	0·84	(0·76–0·90)	<0·001	<0·001
Day 7 stroke	0·61	(0·53–0·67)	0·71	(0·64–0·77)	<0·001	0·76	(0·69–0·83)	<0·001	0·012
Day 28 stroke	0·59	(0·53–0·65)	0·70	(0·64–0·77)	<0·001	0·76	(0·69–0·82)	<0·001	0·004
Day 90 stroke	0·61	(0·55–0·67)	0·71	(0·65–0·76)	<0·001	0·76	(0·71–0·82)	<0·001	<0·001

Table 2: c statistics (with 95% CI) for early stroke discrimination with ABCD2, ABCD2-I, and ABCD3-I scores at each timepoint after transient ischaemic attack

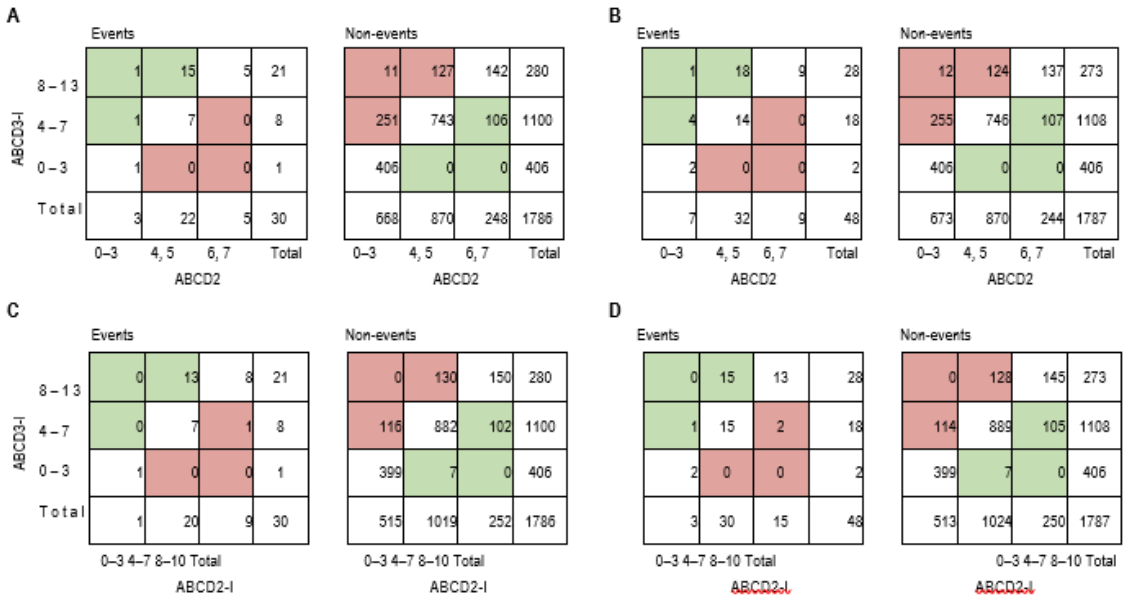

Figure 4: Reclassification of patients from low, medium, and high categories of ABCD2 to ABCD3-I score and ABCD2-I to ABCD3-I score, stratified by stroke events or stroke non-events at 2 days and 7 days after transient ischaemic attack

(A) Risk reclassification at 2 days, ABCD2 to ABCD3-I. (B) Risk reclassification at 7 days, ABCD2 to ABCD3-I. (C) Risk reclassification at 2 days, ABCD2-I to ABCD3-I. (D) Risk reclassification at 7 days, ABCD2-I to ABCD3-I. White squares indicate no change in risk classification across scores. Green squares indicate improved risk classification by the ABCD3-I score (ie, higher risk assigned to patients who subsequently had a stroke event, or lower risk assigned to patients who subsequently had no event). Red squares indicate worse risk classification by the ABCD3-I score (ie, lower risk assigned to patients who subsequently had a stroke event, or higher risk assigned to patients who subsequently had no event).

Discussion

The results from this pooled analysis of individual-patient data from cohort studies showed that both ABCD2-I and ABCD3-I scores had better predictive ability than the ABCD2 score, but that ABCD3-I was better than ABCD2-I for stroke risk prediction. Our results also confirmed the role of minor ischaemic injury on diffusion-weighted MRI, carotid stenosis, and recent earlier transient ischaemic attack as strong independent predictors of early stroke risk. To the best of our knowledge, this is the first large-scale study with sufficient power to allow robust validation and direct comparison of the prognostic utility of imaging-based scores.

The overall risk of early stroke after transient ischaemic attack in our study was low (1% at 2 days and 2% at 7 days), consistent with other studies in which stroke specialists provided early treatment.[1,9] However, our cohort contained subgroups of patients with high residual risk despite high rates of early antiplatelet and statin treatment. Compared with the ABCD2 score, both imaging-based scores improved identification of these high-risk patients. However, the ABCD3-I score further improved discrimination of high-risk patients compared with the ABCD2-I score. When categorised, the 2 day stroke risk in the highest ABCD3-I group was 7·0%, compared with 3·5% in the corresponding ABCD2-I group (figure 2). At 7 days, stroke risks in the highest score categories were 9·3% for ABCD3-I compared with 5·7% for the ABCD2-I score (figure 2). Because the risk of stroke is highest within the first days after transient ischaemic attack, prognostic models for early risk prediction with optimal discrimination at very early timepoints such as within 2 days are likely to have greatest utility for decision making for individual patients in clinical practice.

In addition to discrimination, risk reclassification is an important measure of the validity of new prognostic risk scores when new variables are added to an existing score. Across their entire range, both ABCD2-I and ABCD3-I scores improved the classification of patients according to early stroke risk when compared with the ABCD2 score (net reclassification improvement). However, measures of risk reclassification across the entire range of a prognostic score have little application in routine practice, where clinicians often make treatment decisions based on risk categories defined by thresholds. When defined by risk categories (CNRI) and compared with ABCD2, only the ABCD3-I score improved reclassification of patients into appropriate high-risk and low-risk groups. Furthermore, the ABCD3-I score substantially improved risk reclassification compared with the ABCD2-I score, with greatest improvement in risk assignment for very early stroke recurrence. Compared with the ABCD2 score, the ABCD3-I score correctly reclassified as high risk an additional 57% (17/30 patients) of patients who had stroke at 2 days, at a net cost of inappropriate classification of an additional 14% (389/2013 patients) of patients who did not have stroke (figure 4A).

The ABCD3-I score was well calibrated, which suggests that the risk recorded in the independent validation sample was consistent with risk expected with the patients included in the earlier derivation study.[9] This consistency is an important consideration for clinical use, where estimates of risk for individual patients must be reliable for safe triage decisions to different treatment pathways. By contrast, stroke risk was consistently overestimated at all levels of the ABCD2-I score, suggesting poor calibration. In addition to prognostic utility of ABCD3-I in transient ischaemic attack defined by time-based traditional criteria, the score improved discrimination of early stroke risk in patients with tissue-defined transient ischaemic attack without ischaemic injury on diffusion-weighted MRI, and in those with transient symptoms and minor diffusion-weighted MRI abnormality (ie, transient symptoms with infarction).

Substantial international variation exists in clinical practice and policies for hospital admission for patients with transient ischaemic attack. Although a few centres have implemented urgent MRI-based assessment protocols,[27] substantial variation also exists in the timing and method of brain and vascular imaging after transient ischaemic attack. International guidelines also differ in their recommendations for brain and vascular imaging after transient ischaemic attack, with imaging either immediately or several days after symptom onset, and brain imaging by either CT or MRI recommended.[20,28–31] Our findings provide strong evidence to support an approach of stroke-specialist assessment for patients with focal symptoms consistent with transient ischaemic attack, followed by brain MRI and vascular imaging without delay. With appropriate acute treatment, our data suggest that most patients will have an early stroke risk of about 1%, which might allow safe management in outpatient settings. Some higher-risk patients (7 day risk approximately 9%) might benefit from hospital admission, where they can have immediate access to early thrombolysis, thrombectomy, carotid revascularisation, or other treatment. However, the acceptability of this approach depends on the perceptions and values of stakeholders, as even a 1% risk can be deemed unacceptably high by some patients and physicians.

Our data might also be useful for the design of clinical trials targeting the subgroup of patients at highest residual risk despite modern medical treatment. For example, a randomised trial of a new intervention with anticipated 30% risk reduction of early stroke in unselected patients after transient ischaemic attack treated with standard care would require 17 492 patients, based on the 7 day risk of 2% recorded in our study. However, if targeted to the higher-risk patients with ABCD3-I score ≥8 (7 day risk 9%), the required sample size for a clinical trial of the same intervention with equivalent risk reduction would be 4216 patients.

Strengths of our analysis include its large sample size, inclusion of patient-level data with stroke-specialist confirmed transient ischaemic attack, high rates of contemporary treatments including statins and anti-platelet agents, detailed comparisons of imaging-based scores, and inclusion of patients with time-defined and tissue-defined transient ischaemic attack. Our data are generalisable to patients with mainly anterior circulation transient ischaemic attack who have MRI done within 1 week of symptoms and before recurrent stroke and are treated by hospital-based stroke specialists. We excluded patients who did not have MRI, and those in whom MRI was done after stroke recurrence, some of whom were treated in community settings. These community-treated patients had a higher risk of early stroke recurrence in our cohort, consistent with other studies.

Our study has some limitations. As a pooled analysis of cohort studies, a common protocol was not used for data acquisition, outcomes were not adjudicated centrally, investigators were not masked to exposure variables, and some variation in treatment might exist between included cohorts. Among centres included in our analysis, rates of dual transient ischaemic attack, abnormal diffusion-weighted MRI, and carotid stenosis varied widely (appendix pp 5, 6). We cannot exclude the possibility that centre-specific variables (eg, treatment) might affect early stroke risk. However, treatment after -transient ischaemic attack was not associated with early stroke risk in our study. When we further explored for the effect of study centre by including a centre variable with ABCD2, dual transient ischaemic attack, positive diffusion-weighted MRI, and carotid stenosis in multivariable models of early stroke risk, our findings were unchanged. As the ABCD2-I score was not derived using a probability model, for analysis of calibration it was not possible to apply a model to calculate observed probabilities in our validation set. Therefore, we compared the observed and expected risks at each ABCD2-I and ABCD3-I score stratum, using the risk estimates described in the original derivation papers.[8,9] Because MRI scans were not centrally analysed, we were unable to analyse complex MRI variables that might add further prognostic information. As our study probably included few patients with posterior circulation transient ischaemic attack or younger adults with less common causes of transient ischaemic attack (eg, arterial dissection), the validity of imaging-based scores remains to be established in these groups.[32]

Since Fisher's original descriptions of transient ischaemic attacks,[33] clinicians have sought to identify which episodes are associated with the highest risk of subsequent stroke. Our study provides the strongest evidence so far that the combination of brain MRI, vascular imaging, and clinical features can distinguish patients at highest risk of early stroke after transient ischaemic attack. Although both imaging-based scores showed validity, the extra information provided by the inclusion of carotid stenosis and recurrent transient ischaemic attacks provided improved risk prediction in the ABCD3-I model. Further research is needed to investigate the additional prognostic utility of blood biomarkers, intracranial stenosis, and other imaging markers of stroke risk such as perfusion-weighted MRI. Further research is also needed to study the association between the ABCD3-I score and recurrence risk estimator, which incorporates clinical and detailed MRI variables to predict early recurrence after stroke. Introduction of risk-based transient ischaemic attack management guided by ABCD3-I with immediate stroke-specialist assessment, urgent MRI, and vascular imaging should now be considered, with monitoring of safety, benefits, and cost-effectiveness in practice.[34,35]

Contributors

PJK is the principal investigator of the north Dublin transient ischaemic attack and BIO-transient ischaemic attack studies, planned the study design, and contributed to data acquisition, data analysis, and manuscript preparation. AM planned the study design and contributed to data acquisition, data management, data analysis, and manuscript preparation. CW contributed to data analysis and manuscript preparation. MKa as principal investigator of the COSMOS cohort and CoRisk cohort contributed to the acquisition of data, data management, and preparation of this manuscript. GMDM as principal investigator of the CoRisk cohort contributed to the acquisition of data, data management, and preparation of this manuscript. GWA, AC, JF, PG, LL, J-MO, FP, NR, MKn, JSK, E-JL, PMR, VKS, BS, GT, and YX contributed to the acquisition of data and preparation of the manuscript. All authors have seen and approved the final version of the manuscript.

Declaration of interests

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