Title:

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

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Authors contributions

PJK is the principal investigator of the North Dublin TIA and BIO-TIA 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 statistical analysis and manuscript preparation. MK as PI of the COSMOS cohort and CoRisk cohort contributed to the acquisition of data, data management and to the preparation of this manuscript. GMDM as Principal Investigator of the CoRisk cohort contributed to the acquisition of data, data management and to the preparation of this manuscript. GWA, AC, JF, PG, LL, JMO, FP, NP, JSK, EJL, PMR, VKS, BS, GT, YX, contributed to the acquisition of data and to the preparation of the manuscript. All authors have seen and approved the final version of the manuscript.

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Abstract:

Inclusion of brain imaging alone (ABCD2-I) or recent TIA, brain and carotid imaging (ABCD3-I) with the ABCD2 score may improve risk prediction and stroke prevention after TIA. We aimed to directly compare the validity and prognostic utility of imaging-based stroke risk scores after TIA.

Methods

A pooled analysis of individual-patient data from hospital-based centres was performed. Published and unpublished data from prospective cohort studies of TIA, with high rates of early brain and vascular imaging and follow up were included. Inclusion criteria were (1) Stroke-specialist confirmed TIA (2) Age ≥18 years (3) MRI performed <7 days of index TIA and before stroke recurrence. Multivariable logistic regression was performed to analyse the predictive utility of abnormal diffusion-weighted MRI (DWI), carotid stenosis, and TIA within 1 week of index TIA ('dual TIA') after adjusting for ABCD2 score. The prognostic utility of ABCD2, ABCD2-I and ABCD3-I scores were compared using discrimination, calibration, and risk reclassification metrics.

Results

In 2,415 patients, after adjusting for ABCD2 score, positive DWI ($p=4 \times 10^{-7}$), dual TIA ($p=5 \times 10^{-5}$), and ipsilateral carotid stenosis ($p=3 \times 10^{-9}$) were associated with 7-day stroke after index TIA. 7-day stroke risk increased with increasing ABCD2-I ($p=1x10^{-5}$) and ABCD3-I scores ($p=4x10^{-12}$). Discrimination to identify early stroke risk was improved for ABCD2-I versus ABCD2 (2-day c-statistic 0.75 versus 0.65, p=0.008). However, discrimination was further improved by ABCD3-I compared with ABCD2 (c-statistic 0.85 versus 0.65, p<0.001, 2 days) and ABCD2-I (c-statistic 0.85

versus 0.75, p<0.001, 2 days). Early stroke risk reclassification was improved by ABCD3-I compared with ABCD2-I score (clinical net reclassification improvement 35.1% at 2 days).

Conclusion:

Although ABCD2-I and ABCD3-I showed validity, the ABCD3-I score reliably identified highest-risk patients after TIA with improved risk prediction compared with ABCD2-I. TIA 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.

Introduction:

Transient ischaemic attack (TIA) is associated with high risk of early subsequent stroke[1]. However, this risk is not uniform, and depends upon clinical characteristics, underlying pathophysiology, and early treatment of affected patients. Accurate identification of patients at highest risk after TIA is essential to target acute treatment safely and effectively, and to prevent early recurrent stroke.

Following earlier descriptions of simple clinical variables which were associated with increased stroke risk after TIA, the ABCD2 (age, blood pressure, clinical syndrome, duration, diabetes mellitus) prediction score was derived to improve risk stratification of patients with transient neurological symptoms[2-4]. Although externally-validated, the ABCD2 score was originally intended to aid clinical management of patients assessed by non-specialists in community and emergency department settings, and has limited specificity when used by hospital-based stroke specialists[5-7].

To guide risk-based treatment decisions following stroke-specialist assessment, the ABCD2 score has been extended to include imaging findings in the ABCD2-I (brain imaging only) and ABCD3-I (recent earlier 'dual' TIA, carotid imaging, and brain imaging) scores[8,9] (Table 1). Improved discrimination of high-risk TIA patients was observed with both imaging-based scores compared with the ABCD2 score in the original derivation cohorts, supporting their potential to improve the accuracy of early stroke risk prediction. However, several issues remain to be clarified before the scores may be considered for wider use. First, few validation studies of imaging-based scores have been performed, with limitations such as

small sample sizes and inclusion of patients imaged with brain CT, which has lower sensitivity for detection of minor ischaemic change after TIA symptoms[9-15]. Second, it is unclear whether the inclusion of information on earlier TIA 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[16-18]. Validation studies in large samples with early brain MRI and vascular imaging with direct comparisons of imaging-based scores are required to resolve these questions.

We aimed to analyse the external validity and directly compare the prognostic utility of imaging-based stroke risk scores after TIA in a pooled sample of individual patients from international prospective cohort studies.

Methods:

Patient sample:

Hospital-based centres with large TIA patient cohorts, early DWI, other ABCD3-I score components, and complete or near-complete early follow up were identified from published studies and lead investigators invited to include published data from individual patients for analysis. Investigators were also invited to contribute unpublished data, if available.

Inclusion criteria and data abstraction:

Pre-defined inclusion criteria were: (1) TIA confirmed by a stroke specialist (2) Age 18 years or greater (3) Brain MRI information available within 7 days of TIA onset and before stroke recurrence. Patients were excluded if an alternative diagnosis other than TIA was reached, or if they first sought medical attention and/or had brain imaging for a stroke recurrence rather than the index TIA.

Standard definitions of all variables were provided to all centres prior to data abstraction. Data was abstracted from existing TIA registries at each individual centre using a standardised electronic template, de-identified, and collated centrally. Decisions relating to early treatment and hospital admission at each centre were at the discretion of the treating clinician in this observational study.

For comparison with the original ABCD2-I and ABCD3-I validation samples and external validation studies, the World Health Organisation clinical definition of

TIA was used: an acute loss of focal cerebral or ocular function lasting less than 24 hours, without an apparent non-vascular cause[19]. The prognostic utility of the imaging-based scores was assessed in 'tissue-defined' TIA as proposed by the American Stroke Association in a pre-specified secondary analysis[20].

The index TIA for study inclusion was defined as that most recently preceding stroke specialist assessment. 'Dual TIA' was defined as the occurrence of at least two TIAs, the index TIA and one other TIA's in the 7 days prior to the index event. For standardisation and generalisability, stroke was defined as a new neurological deficit fitting the WHO stroke definition, which occurred after complete resolution of symptoms of the preceding TIA (Web-supplement).

Atrial fibrillation (AF) was defined as pre-existing or newly-detected AF by ECG and/or continuous cardiac rhythm monitoring following TIA. Carotid stenosis was defined as ≥50% narrowing of the ipsilateral internal carotid artery lumen on carotid imaging (including duplex ultrasound, computerised tomography or magnetic resonance angiogram, or angiography), as interpreted by the reporting physician using the NASCET method[21].

MRI information:

DWI hyperintensity was defined as lesion(s) consistent with acute cerebral ischaemia determined by the treating physician at each centre. DWI artefact 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 performed on 1.5 or 3Tesla scanners, within 7 days of index TIA onset.

Stroke recurrence:

Recurrent stroke within 2, 7, 28, and 90 days after index TIA was determined by in-person assessment, and/or 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.

Ethical aspects:

Local ethics committee and institutional review board approval was obtained at each centre, according to local regulations. Included patients provided informed consent for participation of research into stroke prevention following TIA.

Statistical analysis

Statistical analysis was performed using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Parametric and non-parametric comparisons of categorical and continuous variables were made using chi-squared, t-test and Mann-Whitney tests, as appropriate. All significance tests were two-sided. Multivariable logistic regression analysis of the additional prognostic utility of positive DWI, carotid stenosis, and dual TIA to the ABCD2 score (ie. parameters included in the ABCD2-I and ABCD3-I scores) was performed with 7-day stroke as the dependent variable.

Missing data were addressed via a pre-specified standardised 3-step approach. First, investigators were requested to re-check source datasets for

potential data-point misclassifications. Second, if considered valid based on other available variables, values for missing variables were imputed based on clinical data supplied (eg. if 'MRI done' variable missing, but 'DWI 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, was done using the sub-set (2,064 patients) on 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 (ROC) analysis and the c-statistic (area under curve) calculated at 2 and 7 days after the index TIA[21]. Ideal discrimination produces a c-statistic of 1·0 whereas discrimination which is no better than chance produces a c-statistic of 0·5. Confidence intervals 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 examined 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 Hosmer-Lemeshow chi-squared (χ^2) statistic for each comparison. A χ^2 >20 was interpreted

as indicating poor approximation of observed with predicted risk and thus limited calibration, according to criteria recommended by D'Agostino[23]. Due to low or absent events at the extremes of each score (for example, no events were observed at ABCD3-I scores of 0 or 1), the score strata were collapsed into groups containing sufficient events for calculation of the chi-squared statistic.

Risk reclassification from ABCD2 to ABCD2-I and ABCD3-I scores was examined using 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 [NRI]) was also calculated (Web-supplement)[24-26]. Due to concerns about the validity of hypothesis tests for comparison of risk reclassification by prognostic models, no p-values were calculated[26].

Role of funding source

Funding sources were not involved in the design, conduct, analysis, or reporting of the study findings.

Results:

Clinical characteristics:

Sixteen centres from Europe, United States, and Asia contributed individual-patient data from 3,535 patients with TIA. Of these, 2,415 patients met pre-specified eligibility criteria and were included for analysis. Clinical characteristics are described in Table 2 and web-supplement. Complete data were available for ABCD2 score calculation in 99% (2,392 patients), DWI for TIA evaluation in 96.6% (2,332 patients), carotid imaging in 95.9% (2,315 patients), dual TIA in 91.7% (2,215 patients), and 7-day stroke occurrence in 97.2% (2,347 patients). The median age of included patients was 68 years, 58.5% were male, 20.2% were current smokers, and 13% had atrial fibrillation. DWI hyperintensity after index TIA was present in 29.7%, and carotid stenosis in 13.3% (Table 2).

Early stroke risk:

Stroke after index TIA occurred in 1.4% at 2 days (32 patients) and 2.3% at 7 days (53 patients). When clinical variables included in the ABCD2 score were analysed individually, only motor or speech symptoms were associated with 7-day stroke risk (p value 1×10^{-5}). However, when analysed as an ordinal variable, higher ABCD2 score was associated with greater risk of 7-day stroke (p=0.003, chi-squared test for trend). Smoking, atrial fibrillation, and acute medication use before or after index TIA were not associated with early stroke risk. Ischaemic injury on DWI performed for evaluation of the index TIA ($p=4 \times 10^{-7}$), dual TIA within 7 days of index TIA ($p=5 \times 10^{-5}$), and ipsilateral carotid stenosis ($p=3 \times 10^{-9}$) were associated with greater stroke risk at 7 days and other early time-intervals. (Web-supplement)

On multivariable logistic regression, after adjusting for ABCD2 score, positive DWI remained as an independent predictor of 7-day stroke ($p=1 \times 10^{-5}$). When brain imaging was incorporated with ABCD2 as the ABCD2-I score, 7-day stroke risk increased with increasing ABCD2-I score ($p<0.001$ for linear trend). When ABCD2-I was collapsed into low (0-3), medium (4-7), and high (8-10) categories, 7-day stroke rates were higher with higher risk categories (p for trend 1×10^{-5}).

After adjusting for ABCD2 score, both dual TIA ($p=3 \times 10^{-5}$) and carotid stenosis ($p=4 \times 10^{-9}$) were independent predictors of 7-day stroke. After further adjustment for ABCD2 score and positive DWI (ie. items included in the ABCD2-I score), dual TIA ($p=0.002$) and carotid stenosis ($p=1 \times 10^{-7}$) remained as independent predictors of early stroke risk. When these variables were included together as the ABCD3-I score, 7-day stroke risk increased in a linear fashion with increasing ABCD3-I score ($p=0.0005$ for trend). When patients were classified by ABCD3-I score as low (0-3), medium (4-7), and high (8-13) scores, stroke risk increased with increasing score category (p for trend 4×10^{-12}). In patients with an ABCD3-I score of 0 or 1, no patient had stroke at 7 days, compared with 16.7% risk in those with a score of 12 (no patient had a maximum score of 13).

Direct comparison of discrimination of ABCD2, ABCD2-I, and ABCD3-I scores:

For direct comparison of ABCD2, ABCD2-I, and ABCD3-I scores, data were complete for all exposure variables in 2,128 patients, with complete data for stroke outcome at 2 and 7 days in 2,064 of these. 32 of these patients (1.6%) had stroke at 2 days and 52 (2.5%) at 7 days.

Compared with the ABCD2 score, the ABCD2-I score had greater discrimination to identify TIA patients who had stroke at 2 days (c-statistic 0.75 versus 0.65, p=0.008). However, the ABCD3-I score was superior in discrimination for 2-day stroke, compared with the ABCD2 (c-statistic 0.85 versus 0.65, p<0.001) and ABCD2-I scores (c-statistic 0.85 versus 0.75, p<0.001) (Figure 2). These findings were consistent when the analysis was repeated for stroke at 7, 28, and 90 days (Table 3).

Risk reclassification:

Across the entire range of each score, risk reclassification was improved for each imaging-based score compared with the ABCD2 score. For stroke at 2 days, the net reclassification improvement for the ABCD2-I score was 36.7% (p=0.01) and for the ABCD3-I score was 42.2% (p=0.01). However, for score categories used for clinical decision-making (clinical net reclassification improvement), risk reclassification was improved for the ABCD3-I score (CNRI 43.3%, p=0.02) but not the ABCD2-I score (CNRI 11.5%, p=0.3) (Table 4).

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 68.6% (p<0.001) and the clinical net reclassification improvement was 35.1% (p=0.005). Similar findings were observed for stroke at 7 days (Table 4).

Calibration:

When the observed stroke risk at 7 days for each ABCD3-I score in the pooled validation cohort was compared with expected risk based on the original derivation cohort, the observed risk closely approximated expected risk (Figure 3). The chi-squared statistic was 12.8, indicating good calibration of the score. By contrast, approximation of observed risk with expected risk for the ABCD2-I score was poor, with over-estimation of observed risk at most levels of the score. The chi-squared statistic was 132, indicating poor calibration (Web-supplement).

Potential application in clinical practice:

We examined the distributions of patients with stroke and proportions of the overall cohort when the ABCD3-I score was dichotomised as 0-7 and 8-13, to explore the potential application of a single risk threshold in clinical practice. Although 84% (1,731 patients) of the cohort had ABCD3-I scores of 0-7, the 7-day stroke risk in this group was 1.27% (CI 0.74-1.8%). By contrast, in the 16% of the cohort with ABCD3-I scores of 8 or greater (333 patients), 7-day stroke risk was 9% (CI 5.9-12.1%). Of the 52 patients who experienced stroke at 7 days, 58% (30/52) occurred within the high-risk subgroup (ABCD3-I ≥8), while 42% of stroke outcomes (22 patients) occurred within the much larger group with ABCD3-I <8 (1,731 patients).

When dichotomised, the specificity of an ABCD3-I score of ≥8 for identification of TIA patients who had subsequent stroke at 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%, while the negative predictive value (probability that 7-day stroke will not occur in patients with ABCD3-I 0-7) was 98.7%.

Sensitivity analyses:

We did pre-specified sensitivity analyses to examine the prognostic utility of the scores in patients with American Stroke Association 'tissue-defined' TIA (absence of ischaemic injury on DWI), Asian and non-Asian subgroups, and in those imaged with brain CT but not MRI.

For patients with 'tissue-defined' TIA (by definition DWI negative), the brain imaging item was scored zero and ABCD2-I was equal to ABCD2 score. In this sub-group (1,639 patients), discrimination for the ABCD3-I score was greater for stroke at 2 days (c-statistic 0.83 versus 0.75, p=0.06) and 7 days (c-statistic 0.69 versus 0.63, p=0.058). In the subgroup with clinical TIA but positive DWI ('transient symptoms with infarction', 693 patients), the ABCD3-I score also showed improved discrimination at 2 (c-statistic 0.78 versus 0.52, p<0.001) and 7 days (c-statistic 0.70 versus 0.55, p<0.001).

Discrimination for stroke at 2 and 7 days was also greater with ABCD3-I compared with ABCD2 and ABCD2-I scores in non-Asian cohorts, but the difference was attenuated in the Asian sub-group, possibly related to low statistical power (27 strokes at 7 days in 404 patients). No prognostic 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).

Discussion:

Although some earlier studies have provided useful data on the external validity of the ABCD2-I and ABCD3-I TIA risk scores, we describe the first large-scale study with sufficient power to allow robust validation and direct comparison of the prognostic utility of imaging-based scores. We confirmed the role of minor ischaemic injury on DWI, carotid stenosis, and recent earlier TIA as strong independent predictors of early stroke risk.

The overall risk of early stroke after TIA in our study was low (1.4% at 2 days and 2.3% at 7 days), consistent with other studies where early treatment by stroke specialists was provided[1,9]. However, our cohort contained subgroups of patients with high residual risk despite high rates of early 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%, compared with 3% in the corresponding ABCD2-I group. At 7 days, stroke risks in the highest score categories were 9% for ABCD3-I compared with 5% for the ABCD2-I score. Because the risk of stroke is highest within the first days after TIA, prognostic models for early risk prediction with optimal discrimination at early time-intervals 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 prognostic risk scores which add new variables to existing scores. Across their entire range, both ABCD2-I and ABCD3-I scores improved the distribution 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 limited application in routine practice, where clinicians frequently make treatment decisions based on risk categories defined by thresholds. When defined by risk categories (clinical net reclassification improvement) and compared with ABCD2, only the ABCD3-I score improved reclassification of patients into appropriate high- and low-risk groups. Further, the ABCD3-I score substantially improved risk reclassification when 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 56% of patients who had stroke at 2 days, at a 'cost' of inappropriate classification of an additional 7.6% of patients who did not have stroke.

The ABCD3-I score was well-calibrated, indicating that the risk observed in the independent validation sample was consistent with risk expected based on patients included in the earlier derivation study[9]. This 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 over-estimated at all levels of the ABCD2-I score, indicating poor calibration. In addition to prognostic utility of ABCD3-I in TIA defined by time-based traditional criteria, the score improved discrimination of early stroke risk in 'tissue-defined' TIA

patients without ischaemic injury on DWI, and in those with transient symptoms and minor DWI abnormality ('transient symptoms with infarction').

Substantial international variation currently exists in clinical practice and policies for hospital admission for patients with TIA. Although a few centres have adopted urgent MRI-based assessment protocols[27], significant variation also exists in the timing and method of brain and vascular imaging after TIA. International guidelines also differ in their recommendations for brain and vascular imaging after TIA, with imaging either immediately or several days after symptom onset, and brain imaging by either CT or MRI recommended[20,28-31]. Our data provides strong evidence to support an approach of stroke-specialist assessment for patients with focal symptoms consistent with TIA, followed by brain MRI and vascular imaging without delay. With appropriate acute treatment, our study suggests that most patients will have an early stroke risk of approximately 1%, which may allow safe management in outpatient settings. A minority of higher-risk patients (7-day risk approximately 9%) may benefit from hospital admission, where they may immediately access early thrombolysis, carotid revascularisation, or other treatment.

Our data may 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 TIA treated with standard care would require 17,492 patients, based on the 7-day risk of 2.3% observed 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 4,216 patients.

Strengths of our analysis include its large sample size, inclusion of prospectively-ascertained patient-level data with stroke-specialist confirmed TIA, high rates of contemporary treatments including statins and antiplatelet agents, detailed comparisons of imaging-based scores, and inclusion of time-defined and tissue-defined TIA patients. However, we acknowledge some limitations. As a pooled analysis of prospective observational studies, a common protocol was not used for data acquisition, outcomes were not adjudicated centrally, investigators were not blinded to exposure variables, and some variation in treatment may exist between included cohorts. As our study included few patients with posterior circulation TIA or younger adults with less common causes of TIA (eg. arterial dissection), the validity of imaging-based scores remains to be established in these groups[32].

Since CM Fisher's original descriptions of 'transient ischaemic attacks'[33], clinicians have sought to identify which episodes carry highest risk of subsequent stroke. Our study provides the strongest evidence to date that the combination of brain MRI, vascular imaging, and simple clinical features can distinguish patients at highest risk of early stroke after TIA. Although both imaging-based scores showed validity, the extra information provided by the inclusion of carotid stenosis and recurrent TIAs provided superior 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.

Introduction of risk-based TIA management guided by ABCD3-I with immediate stroke-specialist assessment[34,35], urgent MRI and vascular imaging should now be considered, with monitoring of safety, benefits, and cost effectiveness in practice.

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Item	Definition	ABCD2-I	ABCD3-I
Age	≥60 years	0, 1	0, 1
Blood Pressure	≥140 , ≥90 mm Hg	0, 1	0, 1
Clinical	Unilateral weakness, or speech impairment without weakness	0, 1 (speech impairment), 2 (motor weakness)	0, 1 (speech impairment), 2 (motor weakness)
Duration	≥60, 10–59, or <10 minutes	0 (<10 minutes), 1 (10-59 minutes), 2 (≥60 minutes)	0 (<10 minutes), 1 (10-59 minutes), 2 (≥60 minutes)
Diabetes Mellitus	Diabetes mellitus present	0,1	0,1
Dual TIA	TIA prompting medical attention, plus at least one other TIA in the preceding 7 days	Not applicable	0, 2
Imaging - Brain	Acute DWI hyperintensity	0,3	0, 2
Imaging - Carotid	Ipsilateral ≥ 50% stenosis of internal carotid artery by duplex ultrasound, or angiography	Not applicable	0, 2
Total		**0–10**	**0–13**

Table 1: ABCD2-I and ABCD3-I imaging based scores for risk prediction after TIA

		N (%)
Risk factors	Male gender	1411/2413 (58·5)
	Age, years (median, IQR)	68 (57-77)
	Hypertension	1609/2384 (67.5)
	Hyperlipidaemia	818/1952 (41·9)
	Atrial Fibrillation	302/2327(13·0)
	Dual TIA	458/2215 (20·7)
	Current Smoker	475/2346 (20·2)
	Coronary Artery Disease	311/2111 (14·7)
	Carotid stenosis	309/2315 (13·3)
	Diabetes Mellitus	397/2410 (16·5)
	Post TIA Statin	1332/1795 (74·2)
	Post TIA Anti-platelet or anti-coagulant	1719/1830 (93.9)
ABCD2 score (median, IQR)		4 (3-5)
Stroke recurrence	2 days	32/2324 (1·4)
	7 days	53/2347 (2·3)
	28 days	66/2305 (2·9)

90 days	86/ 2247 (3·8)	

Table 2: Clinical characteristics of pooled sample, n=2415

	ABCD2	ABCD2-I	p (ABCD2-I vs ABCD2)	ABCD3-I	p (ABCD3-I vs ABCD2)	p (ABCD3-I vs ABCD2-I)
Day 2 stroke	0·65 (0.57-0.72)	0·75 (0.68-0.81)	0·002	0·85 (0.78-0.91)	<0·001	<0·001
Day 7 Stroke	0·61 (0·54–0·68)	0·71 (0·64–0·77)	0·001	0·76 (0·69–0·83)	<0·001	0·006
Day 28 Stroke	0.60 (0.53-0.65)	0.70 (0.63-0.76)	<0.001	0.76 (0.69-0.81)	<0.001	0.002
Day 90 Stroke	0.61 (0.55-0.67)	0.70 (0.65-0.75)	0.001	0.76 (0.71-0.82)	<0.001	<0.001

Table 3: C-statistics (with 95% confidence intervals) for early stroke discrimination with ABCD2-I and ABCD3-I scores compared with ABCD2 score and together, at each time interval following TIA

Day of recurrent stroke	Re-classified from	Re-classified to	Clinical NRI Events %	Clinical NRI Non events	Clinical NRI Overall (%) ADD

			(CI)	% (CI)	CIs
2	ABCD2	ABCD2-I	18·6 (5·2 to 32·3)	-7·3 (-6·2 to -8·3)	11·5
2	ABCD2	ABCD3-I	59·4 (42·0 to 76·0)	-16·0 (-14·4 to -17·.6)	43·3
2	ABCD2-I	ABCD3-I	43·8 (26·6 to 60·9)	-8·7 (- 7·5 to - 10·0)	35·1
7	ABCD2	ABCD2-I	17·0 (6·8 to 27.1)	-7·7 (-6.6 to -8·9)	9·2
7	ABCD2	ABCD3-I	48·1 (34·5 to 61·7)	-16·1 (-14·5 to -17·7)	32·0
7	ABCD2-I	ABCD3-I	30·8 (18·2 to 43·3)	-8·4 (-7·2 to -9·6)	22·4

Table 4: Risk reclassification from ABCD2 to ABCD2-I and ABCD3-I scores, and from ABCD2-I to ABCD3-I scores. CNRI= Clinical net reclassification improvement for risk categories. Positive values indicate improved reclassification across scores. Clinical categories: ABCD2 low (0-3), medium (4,5), high (6,7); ABCD2-I low (0-3), medium (4-7), high (8-10); ABCD3-I low (0-3), medium (4-7), high (8-13)