National Institute for Health and Care Excellence

1

Draft for consultation

Stroke (update)

Evidence review B: transient ischaemic attack (TIA) prediction rules

NICE guideline

Prognostic evidence review

November 2018

Draft for consultation

This evidence review was developed by the National Guideline Centre

1

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1

1 Risk prediction scores

1.1 Review question: How accurately do scoring systems predict the risks of future ischaemic stroke or transient ischaemic attack (TIA) within the first 7 days in people with suspected TIA?

1.2 Introduction

Patients who have experienced a TIA are at increased risk of having a stroke in the days and weeks following the TIA. Scoring systems have been developed to stratify TIA patients according to their individual future risk of stroke or TIA. The results of these TIA risk scoring systems have been used to guide decisions about the rapidity of access to specialist assessment following a TIA; however these tools are not applied consistently in practice. The committee considered how accurately these scoring systems predicted the risk of stroke or TIA in the first seven days following a TIA and whether these should be used to guide current practice.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 16 with suspected TIA
Risk tool	Validated risk stratification tools/scoring systems (ABCD2 and other variants e.g. ABCD2-I, ABCD3, ABCD3-I)
Target condition	Stroke or TIA within 7 days
Outcomes	Discrimination (area under curve [c statistic]) Calibration (R^2, Brier Score, Hosmer-Lemeshow test statistic; Somers' D statistic), Calibration plot Reclassification <u>These will be assessed for the following outcomes:</u> <u>Critical</u> Risk of stroke (stroke at 24 hours, 72 hours and 7 days) Mortality (7 day) <u>Important</u> Functional outcomes – modified Rankin scale (mRS) 90 days and 1 year Quality of life
Study design	Prospective observational studies Systematic reviews and meta-analyses of the above Exclusions: derivation studies/internal validation studies

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[19] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy upto March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

Risk of bias was assessed using the prediction study risk of bias assessment tool (PROBAST) risk of bias checklist for primary studies or the ROBIS checklist for systematic reviews, including individual patient data (IPD) meta-analyses. IPD analyses were included in the same way as published systematic reviews, with the outcomes reported as described in the IPD analysis and risk of bias assessed for the IPD analysis per outcome.

Note that this question is an update and included in the previous guideline. Search strategies run from 2008 onward. The previous guideline included 4 studies,[10, 42, 74, 82] none of which meet the protocol for this review. Three of these studies related to the ABCD score, and one was a derivation study for ABCD2.

For risk prediction tools ideal discrimination produces a C statistic of 1·0, whereas discrimination that is no better than chance produces a C statistic of 0·5.

1.5 Clinical evidence

1.5.1 Included studies

Two individual patient data (IPD) analyses were identified for this review, both from the same multicentre authors.[52, 59] The first study from Merwick et al., 2010[52] consists of a derivation sample from 8 papers,[7, 11, 22, 23, 50, 54, 66, 68] and a validation sample from population-based studies in Dublin[23, 78] and Oxford,[13] plus additional unpublished data. The derivation cohort was used to derive the ABCD3 and ABCD3-I scores and therefore only the pooled individual patient data for ABCD2 scores have been included from this cohort, excluding the derivation data as per protocol. The validation sample consists of population based studies that the authors note are more likely to be treated later, treated by non-specialists, and have higher recurrent stroke risk than those in hospital-based studies. These cohorts were used for validation of the ABCD2, ABCD3 and ABCD3-I scores.

The second paper from Kelly et al., 2016[46] is a validation study of the prediction rules using pooled individual patient data from 16 cohort studies across 13 papers[1, 17, 27, 30, 32, 45, 51-53, 57, 67, 73, 79] and additional unpublished data. These cohorts were used for validation of the ABCD2, ABCD2-I, and ABCD3-I.

Details for each of the included risk stratification tools are detailed in Table 2.

Although some retrospective data may have been included in the IPD analyses the majority of included studies for the validation cohorts are prospective and given the benefits of IPD analysis it was agreed to include these findings despite the potential for some retrospective data being included.

The included studies are summarised in Table 3 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

It is noted that the population differs slightly from our protocol as these studies include those with TIA, rather than those suspected with TIA, with the exception of 1 study[6]. Data from the OXVASC study population were included in both of the IPD analyses but it was not possible to be certain about the degree of overlap in the samples. Data from the earlier Merwick study was also included in the Kelly study, but the overalp in the sample was approximately 10% and it was decided to be acceptable to include both reviews to avoid losing large amounts of

data. Also of note is that the inclusion criteria in Kelly et al., 2016[59] as they selected only those who had an MRI within 7 days of TIA onset and before stroke occurrence. Outcomes for ABCD2 in the Kelly study have been downgraded for selection bias, whereas outcomes for risk tools that require imaging have not been downgraded.

Five additional prospective cohorts were included, all of which evaluated the discriminative ability of the ABCD2 score.

See also the study selection flow chart in appendix C and study evidence tables in appendix D.

Table 2: Risk score items and definitions

Item	Definition	ABCD2	ABCD2-I	ABCD3	ABCD3-I
Age	≥ 60 years	0, 1	0, 1	0, 1	0, 1
Blood pressure	≥140, ≥90 mm Hg	0, 1[(a)]	0, 1[(a)]	0, 1[(a)]	0, 1[(a)]
Clinical	Unilateral weakness, or speech impairment without weakness	0, 1 (speech impairment), 2 (motor weakness)	0, 1 (speech impairment), 2 (motor 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)	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	0,1	0,1
Dual TIA	TIA prompting medical attention, plus at least one other TIA in the preceding 7 days	N/A	N/A	0, 2	0, 2
Imaging - Brain	Acute DWI hyperintensity	N/A	0, 3	N/A	0, 2
Imaging - Carotid	Ipsilateral ≥ 50% stenosis of internal carotid artery by duplex ultrasound, or angiography	N/A	N/A	N/A	0, 2
Total range		**0-7**	**0–10**	**0 - 9**	**0 - 13**

(a) Coded as 1 if either systolic blood pressure ≥140mmHg or diastolic ≥90mmHg.

1.5.2 Excluded studies

See the excluded studies list in appendix F.

1.5.3 Summary of clinical studies included in the evidence review

Table 3: Summary of studies included in the evidence review

Study	Risk tool	Population	Outcomes	No of events	Limitations
Merwick 2010[52]	ABCD2 ABCD3 ABCD3-I	**Derivation cohort** (IPD): n=2654 8 cohorts from Europe and North America **Validation cohort** (2 population based cohorts): n=1232 2 centres UK and Ireland TIA confirmed by a stroke specialist, age >18 years, or DWI done within 7 days of TIA (28 days for validation cohort).	C statistic 2 day stroke 7 day stroke	Stroke recurrence: Derivation cohort 2 day 24/2362 (1%) 7 day 45/2366 (2%) Validation 7 days 92/1232 (7%)	Some data obtained from registries unclear if prospective or retrospective data
Kelly 2016[46]	ABCD2 ABCD2-I ABCD3-I	16 Cohorts: n=2176 Europe, USA, Asia TIA confirmed by a stroke specialist, age >18 years, and MRI done within 7 days of TIA onset	C statistic 2 day stroke 7 day stroke	Stroke recurrence: 2 day 30/2085 (1%) 7 day 49/2108 (2%)	Some data obtained from registries unclear if prospective or retrospective data
Asimos 2010 [6]	ABCD2	Validation cohort Presumptive diagnosis of TIA (sudden focal loss of neurologic function involving the brain or retina with complete recovery within 24 hours).	C statistic 7 day stroke	Stroke occurrence 7 day: 373/1667 (22.4%)	Non-consecutive enrolment and , no other performance measures evaluated (for example, calibration or reclassification)
Tsivgoulis 2010 [83]	ABCD2	Validation cohort TIA patients hospitalised and diagnosed according to the WHO criteria	C statistic 7 day stroke	Stroke occurrence 7 day: 12/148 (8.1%)	No other performance measures evaluated (for example, calibration or reclassification) and few events per predictor
Perry 2011 [65]	ABCD2	Validation cohort Adults with a final diagnosis of transient ischemic attack or minor stroke at the emergency department	C statistic 7 day stroke	Stroke occurrence 7 day: 38 (1.8%)	No other performance measures evaluated (for example, calibration or reclassification) and few events per predictor
Ghandeh ari 2012	ABCD2	Validation cohort TIA or minor	C statistic	Stroke occurrence	No other performance

Study	Risk tool	Population	Outcomes	No of events	Limitations
[33]		ischaemic stroke patients diagnosed by a neurologist, presenting within 24 hours from symptom onset and a pre-morbid mRS of ≤1	3 day stroke	3 day: 132/393 (34%)	measures evaluated (for example, calibration or reclassification)
Ozpolat 2013 [62]	ABCD2	Validation cohort Adults with TIA diagnosed by a neurologist	C statistic 3 day stroke	Stroke occurrence 3 day: 8/64 (12.6%)	No other performance measures evaluated (for example, calibration or reclassification)

1 See appendix D for full evidence tables.

2

3

1.5.4 Quality assessment of clinical studies included in the evidence review

1.5.4.1 Discrimination

Table 4: Clinical evidence profile: Risk scores for predicting future stroke, Merwick 2010

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	C statistic (95% CI)	Quality
ABCD2 - IPD 2 day	1 (8 cohorts)	2654	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0.71 (0.62 - 0.77)	MODERATE
ABCD2 - IPD 7 day	1 (8 cohorts)	2654	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0.71 (0.64 - 0.77)	MODERATE
ABCD2 - IPD, 7 day	1 (2 cohorts)	1232	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	0.63 (0.56 - 0.69)	LOW
ABCD3 - IPD, 7 day	1 (2 cohorts)	1232	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	0.64 (0.58 - 0.71)	LOW
ABCD3-I -IPD, 7 day	1 (2 cohorts)	1232	Serious risk of bias[c]	No serious inconsistency	No serious indirectness	No serious imprecision	0.71 (0.63 - 0.78)	MODERATE

(a) Downgraded by 1 increment for risk of bias (selection bias as only included those with imaging data and unclear risk of bias of included studies).
(b) Downgraded by 2 increments for risk of bias (validation sample not systematically derived, plus selection bias as only included those with imaging data and unclear risk of bias of included studies).
(c) Downgraded by 1 increment for risk of bias (validation sample not systematically derived, plus unclear risk of bias of included studies.

Table 5: Clinical evidence profile: Risk scores for predicting future stroke, Kelly 2016

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	C statistic (95% CI)	Quality
ABCD2 - IPD, 2 day	1 (16 cohorts)	2176	Very serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0.64 (0.56 - 0.71)	LOW
ABCD2 - IPD, 7 day	1 (16 cohorts)	2176	Very serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0.61 (0.53 - 0.67)	LOW
ABCD2-I - IPD, 2 day	1 (16 cohorts)	2176	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	0.74 (0.67 - 0.80)	MODERATE
ABCD2-I - IPD, 7 day	1 (16 cohorts)	2176	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	0.71 (0.64 - 0.77)	MODERATE
ABCD3-I - IPD, 2 day	1 (16 cohorts)	2176	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	0.84 (0.76 - 0.90)	MODERATE
ABCD3-I - IPD, 7 day	1 (16 cohorts)	2176	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	0.76 (0.69 - 0.83)	MODERATE

(a) Downgraded by 2 increments for risk of bias (high rate of missing data, plus selection bias as only included those with imaging data and unclear risk of bias of included studies)

(b) Downgraded by 1 increment for risk of bias (high rate of missing data, plus unclear risk of bias of included studies)

Table 6: Clinical evidence profile: Risk scores for predicting future stroke or TIA, prospective cohort studies

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	C statistic (95% CI)	Quality
ABCD2 -, 3 day	1	393	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0.59 (0.53-0.66)	MODERATE
ABCD2 -, 3 day	1	64	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	0.76 (0.64-0.86)	VERY LOW
ABCD2 -, 7 day	1	1667	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	0.59 (0.56-0.62)	MODERATE
ABCD2 -, 7 day	1	148	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	0.72 (0.57-0.88)	VERY LOW

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	C statistic (95% CI)	Quality
ABCD2 -, 7 day	1	2056	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Calculated by enrolling physician: 0.56 (0.47-0.65) Calculated by co-ordinating centre: 0.65 (0.58-0.73)	LOW

(a) Downgraded by 1 increment for risk of bias (analysis method)
(b) Downgraded by 2 increments for risk of bias (analysis method and sample size)
(c) Downgraded by 1 increment based on the width of the 95% confidence interval

1.5.4.2 Calibration

Both IPD studies reported calibration scores. A score of <20 indicates a well-calibrated tool and >20 indicates poor calibration.[25]

Table 7: Clinical evidence profile: Calibration of risk tools

Risk tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	χ^2 statistic	Quality
ABCD3	1 (8 cohorts)	2654	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Not estimable	>20	MODERATE
ABCD2-I	1 (16 cohorts)	2176	Serious risk of bias[a]	No serious inconsistency	No serious indirectness	Not estimable	93.9	MODERATE
ABCD3-I	1 (8 cohorts)	2654	Serious risk of bias[a]	Serious[b]	No serious indirectness	Not estimable	>20	LOW
ABCD3-I	1 (16 cohorts)	2176	Serious risk of bias[a]	Serious[b]	No serious indirectness	Not estimable	17.9	LOW

(a) Downgraded by 1 increment for risk of bias
(b) Downgraded by 1 increment for inconsistent findings between studies (good and poor calibration).

1.5.4.3 Additional results

The IPD studies both report observed risk of stroke categorised by risk score as low, medium and high risk (high score = high risk), as shown in Table 8. This data is not appropriate to quality assess using GRADE.

Table 8: Risk of stroke stratified by risk score (low, medium and high)

	2 day		7 day	
Risk tool, score	**Events/non events**	**Percentage risk**	**Events/non events**	**Percentage risk**
Merwick 2010[52] validation cohort				
ABCD2, 0 – 3 (low risk)	N/R	N/R	N/R	0.6%
ABCD2, 4 – 5 (medium risk)	N/R	N/R	N/R	2.5%
ABCD2, 6 – 7 (high risk)	N/R	N/R	N/R	4.3%
ABCD3, 0 – 3 (low risk)	N/R	N/R	N/R	1.1%(a)
ABCD3, 4 – 5 (medium risk)	N/R	N/R	N/R	2.5%(a)
ABCD3, 6 – 9 (high risk)	N/R	N/R	N/R	10.7%(a)
ABCD3-I, 0 – 3 (low risk)	N/R	N/R	N/R	0.9%(a)
ABCD3-I, 4 – 7 (medium risk)	N/R	N/R	N/R	4.1%(a)
ABCD3-I, 8 – 13 (high risk)	N/R	N/R	N/R	9.8%(a)
Kelly 2016[46]				
ABCD2, 0 – 3 (low risk)	3/671	0.45%	7/680	1.03%
ABCD2, 4 – 5 (medium risk)	22/892	2.47%	32/902	3.55%
ABCD2, 6 – 7 (high risk)	5/253	1.98%	9/253	3.56%
ABCD2-I, 0 – 3 (low risk)	1/516	0.19%	3/516	0.58%
ABCD2-I, 4 – 7 (medium risk)	20/1039	1.92%	30/1054	2.85%
ABCD2-I, 8 – 10 (high risk)	9/261	3.45%	15/265	5.66%
ABCD3-I, 0 – 3 (low risk)	1/407	0.25%	2/408	0.49%
ABCD3-I, 4 – 7 (medium risk)	8/1108	0.72%	18/1126	1.60%
ABCD3-I, 8 – 13 (high risk)	21/301	6.98%	28/301	9.30%

(a) Data extracted from bar graph using WebPlotDigitizer online software

1.5.4.4 Non-included outcomes

No results were presented in the papers for the other outcomes listed in the protocol (e.g. prediction of 7 day mortality).

1.6 Economic evidence

1.6.1 Included studies

No relevant published health economic studies were identified in the 2017 update searches or in the 2008 guideline.

Original health economic modelling undertaken as part of the 2008 guideline did not specifically address the cost effectiveness of risk stratification tools for people with suspected TIA/minor stroke, but addressed the cost effectiveness of early versus late assessment. While the review question on early versus late assessment has not been updated in the 2017 update of the guideline, the recommendations resulting from this review question have implications for the timing of expert assessment for people with suspected TIA. Therefore, a summary of the health economic model from the 2008 guideline is provided in **Table 9** below and in Health economic evidence tables F. For the full report, see: https://www.nice.org.uk/guidance/cg68/evidence/full-guideline-pdf-196845517.

See also the health economic study selection flow chart in appendix E.

1.6.2 Summary of studies included in the economic evidence review

Table 9: Health economic evidence profile: Non specialist assessment by a GP versus immediate assessment at a stroke unit versus assessment within 7 days at a weekly specialist stroke unit clinic

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
National Clinical Guideline for Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA) (CG68): https://www.nice.org.uk/guidance/cg68/evidence/full-guideline-pdf-196845517	Directly applicable[a]	Minor limitations[b]	Decision tree modelling the effect of the treatment strategies on incidence of stroke within 90 days. Treatment effect due to prescribing of modified release dipyridamole obtained from [87]. People assessed immediately get the benefit from medical treatment immediately, whereas people assessed at the weekly clinic get the effect from day 4. Costs and QALYs estimated over a lifetime time horizon for those who do not experience a stroke, fatal, dependent and independent strokes.	Immediate assessment saves £95 compared with assessment within 7 days [e]	Immediate assessment compared with assessment within 7 days: 0.06 QALYs gained	**Cost effectiveness for all suspected TIA/minor stroke** **ICER (weekly assessment versus GP assessment):** £5,412 **ICER (Immediate assessment versus GP assessment):** £3,332 **ICER (Immediate assessment versus weekly assessment):** Dominant **Cost effectiveness by ABCD² score group** **Optimal strategy at £20,000 per QALY gained threshold:** ABCD² score 0-1: GP	95% CI: NR Probability cost effective (£20K/30K threshold): NR Costs of immediate and weekly assessment were varied in a probabilistic sensitivity analysis. Results were robust across several one-way sensitivity analyses, including: • Impact of including TIA mimics in ratio 1:1 of actual TIA or minor stroke to TIA mimic. • The timing of endarterectomy: For immediate assessment, 50% to 100% of surgery would take place within 2 weeks of TIA. For

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
(UK NHS and Personal Social Services perspective)						assessment ABCD^2 score 2-7: Immediate assessment	assessment at a weekly clinic, 0 to 50% of surgery would take place within 2 weeks of TIA

Abbreviations: 95% CI: 95% confidence interval; HTA: Health Technology Assessment; ICER: incremental cost-effectiveness ratio; pa: probabilistic analysis; QALY: quality-adjusted life years; pa: probabilistic analysis

(a) UK NHS and Personal Social Services perspective

(b) The base case for the model assumes that all people with suspected TIA have a TIA or a minor stroke and so the costs and QALYs associated with TIA mimics are not captured. However, this was explored in a sensitivity analysis. The model is a simple representation, looking at only 90 days after the TIA for the effects of medical treatment and extrapolating from this to get long-term outcomes.

(c) 2007 UK pounds

(d) A dominant treatment option is one that is both less costly and results in better **health** *outcomes than the comparator treatment*

1

1.6.3 Unit costs

Table 10: UK costs of outpatient imaging

Currency Description	Unit Cost
Ultrasound of Carotid Artery	
Ultrasound Scan with duration of less than 20 minutes, without Contrast	£52
Magnetic Resonance Angiography	
Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast	£180
Cardiac Computed Tomography Angiography	
Complex Computerised Tomography Scan	£148
Computed Tomography of Head	
Computerised Tomography Scan, of One Area, without Contrast	£86
Magnetic Resonance Imaging of Head	
Magnetic Resonance Imaging Scan, One Area, without Contrast, 19 years and over	£139

Source: NHS Reference Costs, 2016-2017

1.7 Resource costs

The recommendation made by the committee based on this review (see section 1.9) is likely to have a substantial impact on resources for the NHS in England.

The committee agreed that urgent (within 24 hours) specialist assessment and investigation arranged for people with suspected TIA represents current best practice, but acknowledged that current practice varies widely. Setting up responsive (7-day per week) TIA services in trusts which do not currently offer daily clinics will require significant additional resources. However, there are likely to be downstream cost savings due to prevention of stroke.

Further work is being carried out to quantify the potential resource impact in this area.

1.8 Evidence statements

1.8.1 Clinical evidence statements

- One IPD analysis of 1232 people assessed the discriminative ability of the ABCD2, ABCD3 and ABCD3-I scores for prediction of stroke at 7 days after TIA or minor stroke. All showed poor or moderate discrimination, which was not considered sufficient for the tools to be clinically useful in this setting (Low to Moderate quality).
- One IPD analysis of 2654 people assessed the discriminative ability of the ABCD2 for prediction of stroke at 2 and 7 days after TIA or minor stroke. This showed moderate discrimination, which was not considered sufficient for the tools to be clinically useful in this setting (Moderate quality).
- One IPD analysis assessed the discriminative ability of the ABCD2, ABCD2-I and ABCD3-I in 2176 people across 16 cohort studies. Discrimination to identify early stroke risk was poor for ABCD2 at both 2 days and 7 days (Low quality). ABCD2-I had moderate discriminative ability at 2 and 7 days which ABCD3-I had good and moderate discriminative ability at 2 and 7 days respectively (Moderate quality).

- Five prospective cohort studies in a total of 4328 people with TIA found very poor to moderate discrimination of ABCD2 for stroke risk at 3 or 7 days (Very low to Moderate quality).
- Overall, there was no evidence to suggest that the tools worked better at 2 or 3 days, compared with 7 days except for ABCD3-I.
- The evidence from the IPD analyses suggested that the ABCD3 and ABCD2-I tools had poor calibration (Moderate quality) and there was inconsistency for the ABCD3-I score with 1 study suggesting good and the other suggesting poor calibration for this tool (Low quality).

1.8.2 Health economic evidence statements

- No relevant economic evaluations were identified in the 2017 update searches or in the 2008 guideline.
- Original health economic modelling undertaken for the 2008 guideline found that immediate assessment at a stroke unit dominated assessment within a seven days at a weekly specialist stroke unit clinic. This cost utility analysis was assessed as directly applicable with minor limitations.

1.9 Recommendations

B1. Refer immediately people who have had a suspected TIA for specialist assessment and investigation, to be done within 24 hours of onset of symptoms. [2019]

B2. Do not use scoring systems, such as ABCD2, to assess risk of subsequent stroke. [2019]

1.10 Rationale and impact

1.10.1 Why the committee made the recommendations

Evidence showed that risk prediction scores (ABCD2 and ABCD3) used in isolation are poor at discriminating early risk of stroke after TIA. There was also evidence that calibration of ABCD3 was poor, while no evidence on the calibration of ABCD2 was found. Adding imaging of the brain and carotid arteries to the risk scores (as is done in the ABCD2-I and ABCD3-I tools) modestly improves discrimination. However, appropriate imaging (including MRI) is not available in general practice or for paramedics, two of the key situations where these tools would be used. Arranging specialist assessment less urgently for some people based on a tool with poor discriminative ability for stroke risk has the potential for harm. Therefore, the committee agreed that risk scores should not be used.

The committee agreed, based on their clinical experience and the limited predictive performance of risk scores, that all cases of suspected TIA should be considered as potentially high risk for stroke. Also, as there is no reliable diagnostic test for TIA (the risk stratification tools are not diagnostic tests), it is important to urgently confirm or refute the diagnosis of a suspected TIA with specialist opinion, particularly as in practice a significant proportion of suspected TIA (30-50%) will have an alternative diagnosis.(that is, TIA-mimic). Therefore, it was agreed that everyone who has had a suspected TIA should have specialist assessment and investigation within 24 hours of the onset of symptoms. The committee noted the results of an original cost–utility analysis, which was undertaken for this review question in the 2008 version of the stroke guideline (CG68). The analysis concluded that ‘immediate assessment’ dominated ‘assessment within a week’ for the entire population of suspected TIA, without the use of a risk stratification tool.

The committee noted that having a TIA (or suspected TIA) is a worrying time and most people would prefer to be assessed as soon as possible. Urgent specialist assessment should ensure that people at high risk of stroke are identified early. This would allow the preventative treatment to begin, which should be introduced as soon as the diagnosis of TIA is confirmed.

1.10.26 Impact of the recommendations on practice

The recommendation reflects current best practice of expert assessment in a TIA clinic within 24 hours, irrespective of risk stratification using clinical scoring systems. Everyone with a suspected TIA should be seen within 24 hours, but provision of daily TIA clinics is not universal. Some areas will need to set up daily TIA clinics to provide this best practice service.

This recommendation should not influence the absolute number of people who need to be subsequently assessed in a TIA clinic, but will result in all suspected TIAs being assessed with an equal degree of urgency. There are likely to be challenges in implementation for some areas in providing an adequately responsive 7 day a week TIA clinic (or a suitable alternative 7-day service) where they currently do not exist, although services are already being encouraged to implement TIA clinics 7 days a week. The committee acknowledged that setting up responsive (7-day a week) services in trusts which do not currently offer daily clinics could require significant additional resource and this may result in a substantial resource impact in the NHS in England. However, there are likely to be downstream cost savings due to prevention of stroke.

The recommendation on offering measures for secondary prevention reflects current practice so no change is expected.

1.11 The committee's discussion of the evidence

1.11.1 Interpreting the evidence

1.11.1.1 The outcomes that matter most

Critical outcomes for this review were risk of stroke at 24 hours, 72 hours 7 days and mortality. Important outcomes were identified functional outcome (mRS) and quality of life.

No evidence was identified for functional outcome or quality of life, nor for risk of stroke at 24 hours.

1.11.1.2 The quality of the evidence

The included evidence consists of two individual patient data (IPD) analyses of 26 observational cohorts from both retrospective and prospective studies, and 5 prospective cohort studies rated as very low to moderate quality across outcomes.

The population for the majority of the data was patients with confirmed TIA, rather than suspected cases. However, the evidence was not downgraded for indirectness as it was agreed to be reasonable to extrapolate these findings to the suspected TIA populationThe IPD analyses used data obtained for each person to allow comparison of baseline data, allowed uniform definitions of variables to reduce heterogeneity and obtained additional unpublished data. It is noted that selection bias was present in the IPD analyses as the studies only included patients with full data sets, including imaging, and therefore outcomes for ABCD2 and ABCD3 (the risk scores without imaging criteria) were downgraded for risk of bias. Other risks of bias were also present, including high rates of missing data and unclear risk of bias of included studies.

The large sample size and moderate quality for the ABCD2 results supported the strong recommendation.

1.11.1.3 Benefits and harms

In people with TIA, ABCD2, the most widely used risk score, had a C statistic of 0.56 to 0.76 across the studies for risk of ischaemic stroke at 2, 3 and 7 days. Therefore, the committee considered this tool to be poorly discriminative for early risk of stroke. In addition, the lower limit of the confidence intervals for the C statistic were as low as 0.47, indicating a similar chance of predicting the outcome as tossing a coin. Calibration was not reported for ABCD2. The evidence showed similar predictive ability of the ABCD3 score, which includes the addition of dual TIA to the risk score, and also reports poor calibration for this tool.

Adding imaging of the brain and carotid artery (ABCD2-I and ABCD3-I) to the risk scores showed a small improvement in discrimination of stroke risk, with a C statistic of 0.71 to 0.84 across the studies. However, this still demonstrates only modest discriminative ability and it was noted that although these tools are better at risk prediction than ABCD2, imaging is not currently available in all but one of the settings (i.e. the emergency department [ED]) to which these tools might most usefully apply. The calibration of the prediction rules varied across the risk scores and populations. ABCD2-I and ABCD3 had poor calibration and there was inconsistency for the ABCD3-I score with 1 study suggesting good and the other suggesting poor calibration for this tool.

The committee discussed the potential harm of not identifying those at high risk of stroke and the implications of this, for example the possibility of not receiving preventative treatment, or receiving it later, leading to increased risk of stroke and potentially worse functional outcome or death. However, the committee noted that since the last version of this guideline was produced, provision of daily TIA clinics is much more common and is now accepted best

practice in the UK. Patients with suspected TIA should therefore be seen within 24 hours regardless of their risk as indicated by a risk score. The committee agreed that seeing some patients less urgently based on risk scores had potential for harm because the risk scoring systems are not sufficiently good predictors of risk of stroke.

The committee noted that there was no disadvantage to patients who are at "low risk" in being seen within 24 hours alongside patients at high risk. However, there will be organisational considerations for those services that do not currently have a 7 day TIA clinic provision.

The committee discussed individual predictors of stroke recurrence, such as carotid stenosis (as identified through imaging in the ABCD3-I risk tool) and atrial fibrillation. They believed that wider issues are useful to consider e.g. evidence of recurrent TIA and presence of anticoagulation, and would expect clinicians to take this into account when assessing patients.

In conclusion, the committee therefore did not recommend the use of risk scores, as their discriminative ability for future ischaemic stroke risk and their calibration were not good enough. It is recommended that all those who have had a suspected TIA are assessed in a specialist setting within 24 hours.

1.11.2.8 Cost effectiveness and resource use

No cost effectiveness evidence was identified for the use of scoring systems to assess the subsequent risk of stroke following suspected TIA. The committee considered that risk scoring tools might have an adverse impact on the timing of referral to expert assessment and advanced imaging (MRI / extracranial arterial imaging including doppler USS). In the absence of economic evidence, the committee also considered the unit costs of outpatient CT and MR imaging. The committee highlighted that current best practice has evolved dramatically since the last version of this guideline was produced and people with suspected TIA are increasingly seen within 24 hours in England.

The committee noted, however, that there is variation in current TIA clinic service provision and while people with suspected TIA are increasingly being seen within 24 hours (which represents current best practice), 7-day services are not yet universal. The committee discussed the need to decide how to prioritise which people should be seen earliest in TIA clinics and how to allocate direct access scan slots. As the clinical evidence determined that scoring systems are poorly discriminative for early risk of stroke recurrence, the committee did not feel that use of scoring systems was appropriate for prioritising which people with suspected TIA are prioritised first for expert clinical assessment.

The committee noted that adding imaging of the brain and carotid artery (ABCD2-I and ABCD3-I) increased the C-statistic, improving the risk-prediction capacity of the tool. However, these tools are more costly due to the addition of imaging costs to the costs of administering ABCD2 and ABCD3. Furthermore, the committee noted that access to imaging is not possible in most of the settings in which scoring systems are applied.

The committee also discussed the costs and effects of incorrect risk stratification using scoring systems. People incorrectly assigned as low risk that are in fact at high risk of recurrent stroke might be referred for specialist assessment and undergo imaging later than they should and might experience delays in secondary prevention, increased risk of stroke, worse functional outcome or death. These outcomes would be associated with a reduction in quality of life. The committee considered that, as the C-statistic for ABCD2 was between 0.6 and 0.7, the risk of incorrect risk stratification was high. The committee agreed that all people with suspected TIA are at significant risk of stroke and so should all be seen within 24 hours. With best practice 7-day TIA clinics in place, the current optimal management strategy is not influenced by the use of a scoring system, and therefore their use is not cost effective.

The recommendation not to use scoring systems has implications for implications for the timing of expert assessment for people with suspected TIA. This review question did not consider the cost effectiveness of seeing all people with suspected TIA within 24 hours and the review question on the timing of expert assessment has not been updated in the 2017 update of the guideline. The committee noted the results of an original cost–utility analysis, undertaken in the original version of the stroke guideline (CG68), which considered the cost effectiveness of early versus late assessment of people with suspected TIA. The analysis concluded that 'immediate assessment' was more effective and less costly than 'assessment within a week' for the entire population of suspected TIA, without the use of a risk stratification tool. Immediate assessment remained dominant in a sensitivity analysis which assumed that 50% of those with suspected TIA had TIA mimics, which in practice lies between 30-50%. The committee agreed that urgent (within 24 hours) assessment arranged for people with suspected TIA represents current best practice, but acknowledged that current practice varies widely. The consensus was that TIA services not currently achieving this should be strengthened in order to see all people immediately, aligning with current best practice. The committee acknowledged that setting up responsive (7-day per week) services in trusts which do not currently offer daily clinics could have a substantial resource impact. In conclusion, no cost effectiveness evidence was identified for the use of scoring systems to assess the subsequent risk of stroke following suspected TIA. The committee chose to recommend that urgent (within 24 hours) assessment at a TIA clinic is arranged, irrespective of the risk of recurrent stroke as predicted by scoring systems. This recommendation was informed by the results of a cost–utility analysis which was undertaken in the previous version of this guideline (CG68). The committee anticipates that this recommendation will have a substantial resource impact to the NHS in England.

1.1.23 Other factors the committee took into account

It was noted that anyone who has a suspected TIA is at risk of ischaemic stroke, and that in a service that is able to assess anyone who presents within 24 hours, a tool to risk stratify (triage) patients is not needed. The committee discussed that there is variation around the country in access to TIA clinics and that risk stratification is currently used to prioritise those with a high ABCD2 score for assessment. Whilst the committee considered that risk assessing patients using these tools has been used to help prioritise patients where the service is limited, they thought the scoring systems are not reliable and that it was much more important to set up a suitable 7-day service where one currently does not exist.

This recommendation should not increase the absolute numbers of people who need to receive expert assessment but it does mean that in some areas people may need to be assessed sooner than they currently are.

The committee noted that education about TIA diagnosis was important. The diagnosis is difficult because the symptoms have resolved at the point of assessment and history taking is crucial. This highlights the need for early specialist assessment. Also it is important to realise that having a TIA (or suspected TIA) is a worrying time for the patient and most people would prefer to be assessed as soon as possible.

References

1. Akijian L, Carty F, Thornton J, Grech R, Kavanagh E, Merwick Á et al. Beyond DWI — Emerging candidate MRI biomarkers associated with risk of early stroke after TIA. Journal of the Neurological Sciences. 2013; 333(Supp 1):e245-6

2. Almasi M, Hodjati Firoozabadi N, Ghasemi F, Chardoli M. The value of ABCD2F scoring system (ABCD2 combined with atrial fibrillation) to predict 90-day recurrent brain stroke. Neurology Research International. 2016:8191659

3. Amarenco P, Labreuche J, Lavallee PC, Meseguer E, Cabrejo L, Slaoui T et al. Does ABCD2 score below 4 allow more time to evaluate patients with a transient ischemic attack? Stroke. 2009; 40(9):3091-5

4. Amarenco P, Lavallee PC, Labreuche J, Albers GW, Bornstein NM, Canhao P et al. One-year risk of stroke after transient ischemic attack or minor stroke. New England Journal of Medicine. 2016; 374(16):1533-42

5. Appelros P, Hals Berglund M, Strom JO. Long-term risk of stroke after transient ischemic attack. Cerebrovascular Diseases. 2017; 43(1-2):25-30

6. Asimos AW, Johnson AM, Rosamond WD, Price MF, Rose KM, Catellier D et al. A multicenter evaluation of the ABCD2 score's accuracy for predicting early ischemic stroke in admitted patients with transient ischemic attack. Annals of Emergency Medicine. 2010; 55(2):201-10.e5

7. Ay H, Arsava EM, Johnston SC, Vangel M, Schwamm LH, Furie KL et al. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. Stroke. 2009; 40(1):181-6

8. Bejot Y, Daubail B, Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. Revue Neurologique. 2016; 172(1):59-68

9. Bibok MB, Penn AM, Lesperance ML, Votova K, Balshaw R. Validation of a multivariate clinical prediction model for the diagnosis of mild stroke/transient ischemic attack in physician first-contact patient settings. Health Informatics Journal. 2017; Epublication

10. Bray JE, Coughlan K, Bladin C. Can the ABCD Score be dichotomised to identify high-risk patients with transient ischaemic attack in the emergency department? Emergency Medicine Journal. 2007; 24(2):92-5

11. Calvet D, Touze E, Oppenheim C, Turc G, Meder JF, Mas JL. DWI lesions and TIA etiology improve the prediction of stroke after TIA. Stroke. 2009; 40(1):187-92

12. Canadian Agency for Drugs and Technologies in Health (CADTH). The ABCD2 scoring system for transient ischemic attacks: a review of the diagnostic accuracy and predictive value. Ottawa. Canadian Agency for Drugs and Technologies in Health (CADTH), 2014. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/apr-2014/RC0525%20-%20ABDC2%20%20Final.pdf

13. Chandratheva A, Geraghty OC, Luengo-Fernandez R, Rothwell PM. $ABCD^2$ score predicts severity rather than risk of early recurrent events after transient ischemic attack. Stroke. 2010; 41(5):851-6

14. Chandratheva A, Geraghty OC, Rothwell PM. Poor performance of current prognostic scores for early risk of recurrence after minor stroke. Stroke. 2011; 42(3):632-7

15. Chardoli M, Firoozabadi NH, Nouri M, Rahimi-Movaghar V. Value of ABCD2-F in predicting cerebral ischemic attacks: Three months follow-up after the primary attack. Acta Medica Iranica. 2016; 54(6):391-4

16. Chardoli M, Khajavi A, Nouri M, Rahimi-Movaghar V. Value of ABCD2 in predicting early ischemic stroke in patients diagnosed with transient ischemic attack. Acta Medica Iranica. 2013; 51(9):611-4

17. Chatzikonstantinou A, Wolf ME, Schaefer A, Hennerici MG. Risk prediction of subsequent early stroke in patients with transient ischemic attacks. Cerebrovascular Diseases. 2013; 36(2):106-9

18. Chu T, Yu W, Wang Y, Guo N, He J, Shao Y et al. The ABCD2 score may underestimate the short-term risk of stroke in Chinese population: A meta-analysis. Neuroendocrinology Letters. 2015; 36(3):262-8

19. Chung H, Refoios Camejo R, Barnett D. Alteplase for the treatment of acute ischaemic stroke: NICE technology appraisal guidance. Heart. 2007; 93(12):1616-7

20. Cocho D, Monell J, Planells G, Ricciardi AC, Pons J, Boltes A et al. Rapid diagnosis and treatment of TIA results in low rates of stroke, myocardial infarction and vascular death. Neurologia. 2016; 31(1):18-23

21. Coutts SB, Barrett KM. TIA risk stratification: What an event was and why it happened are more important than a score. Neurology. 2015; 85(4):304-5

22. Coutts SB, Eliasziw M, Hill MD, Scott JN, Subramaniam S, Buchan AM et al. An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischemic attack or minor stroke. International Journal of Stroke. 2008; 3(1):3-10

23. Cucchiara BL, Messe SR, Taylor RA, Pacelli J, Maus D, Shah Q et al. Is the ABCD score useful for risk stratification of patients with acute transient ischemic attack? Stroke. 2006; 37(7):1710-4

24. Cutting S, Regan E, Lee VH, Prabhakaran S. High ABCD2 scores and in-hospital interventions following transient ischemic attack. Cerebrovascular Diseases Extra. 2016; 6(3):76-83

25. D'Agostino RB, Nam B-H. Evaluation of the Performance of Survival Analysis Models: Discrimination and Calibration Measures. Handbook of Statistics. 23: Elsevier. 2003. p. 1-25.

26. Dai Q, Sun W, Xiong Y, Hankey GJ, Xiao L, Zhu W et al. From clinical to tissue-based dual TIA: Validation and refinement of ABCD3-I score. Neurology. 2015; 84(14):1426-32

27. De Marchis GM, Weck A, Audebert H, Benik S, Foerch C, Buhl D et al. Copeptin for the prediction of recurrent cerebrovascular events after transient ischemic attack: results from the CoRisk study. Stroke. 2014; 45(10):2918-23

28. Duca A, Jagoda A. Transient ischemic attacks: Advances in diagnosis and management in the emergency department. Emergency Medicine Clinics of North America. 2016; 34(4):811-35

29. Engelter ST, Amort M, Jax F, Weisskopf F, Katan M, Burow A et al. Optimizing the risk estimation after a transient ischaemic attack - the ABCDE score. European Journal of Neurology. 2012; 19(1):55-61

30. Ferrari J, Knoflach M, Kiechl S, Willeit J, Schnabl S, Seyfang L et al. Early clinical worsening in patients with TIA or minor stroke: the Austrian Stroke Unit Registry. Neurology. 2010; 74(2):136-41

31. Fothergill A, Christianson TJ, Brown RD, Jr., Rabinstein AA. Validation and refinement of the ABCD2 score: a population-based analysis. Stroke. 2009; 40(8):2669-73

32. George PM, Mlynash M, Adams CM, Kuo CJ, Albers GW, Olivot JM. Novel TIA biomarkers identified by mass spectrometry-based proteomics. International Journal of Stroke. 2015; 10(8):1204-11

33. Ghandehari K, Ahmadi F, Ebrahimzadeh S, Shariatinezhad K, Ghandehari K. The ABCD(2) score is highly predictive of stroke in minor ischemic stroke patients. Translational Stroke Research. 2012; 3(2):273-8

34. Ghandehari K, Ahmadi F, Ebrahimzadeh S, Shariatinezhad K, Ghandehari K. Assessment of ABCD2 scale in patients with transient ischaemic attack or stroke. Neurologia i Neurochirurgia Polska. 2012; 46(5):421-7

35. Ghia D, Thomas P, Cordato D, Epstein D, Beran RG, Cappelen-Smith C et al. Low positive predictive value of the ABCD2 score in emergency department transient ischaemic attack diagnoses: the South Western Sydney transient ischaemic attack study. Internal Medicine Journal. 2012; 42(8):913-8

36. Giles MF, Albers GW, Amarenco P, Arsava EM, Asimos AW, Ay H et al. Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. Neurology. 2011; 77(13):1222-8

37. Giles MF, Albers GW, Amarenco P, Arsava MM, Asimos A, Ay H et al. Addition of brain infarction to the ABCD2 Score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. Stroke. 2010; 41(9):1907-13

38. Hotter BA, Lechner JM, Nolte CH, Audebert HJ, Malzahn U, Heuschmann PU et al. ABCD(2) as a screening tool for cerebral infarction on stroke MRI? European Neurology. 2012; 67(5):315-20

39. Ishida K, Kasner SE, Cucchiara B. Inter-rater reliability and misclassification of the ABCD(2) score after transient ischemic attack. Journal of Stroke and Cerebrovascular Diseases. 2015; 24(6):1174-8

40. Jeerakathil T, Shuaib A, Majumdar SR, Demchuk AM, Butcher KS, Watson TJ et al. The Alberta Stroke Prevention in TIAs and mild strokes (ASPIRE) intervention: rationale and design for evaluating the implementation of a province-wide TIA triaging system. International Journal of Stroke. 2014; 9(Suppl A100):135-43

41. Johansson E, Bjellerup J, Wester P. Prediction of recurrent stroke with ABCD2 and ABCD3 scores in patients with symptomatic 50-99% carotid stenosis. BMC Neurology. 2014; 14:223

42. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007; 369(9558):283-92

43. Josephson SA, Sidney S, Pham TN, Bernstein AL, Johnston SC. Factors associated with the decision to hospitalize patients after transient ischemic attack before publication of prediction rules. Stroke. 2008; 39(2):411-3

44. Josephson SA, Sidney S, Pham TN, Bernstein AL, Johnston SC. Higher ABCD2 score predicts patients most likely to have true transient ischemic attack. Stroke. 2008; 39(11):3096-8

45. Katan M, Nigro N, Fluri F, Schuetz P, Morgenthaler NG, Jax F et al. Stress hormones predict cerebrovascular re-events after transient ischemic attacks. Neurology. 2011; 76(6):563-6

46. Kelly PJ, Albers GW, Chatzikonstantinou A, De Marchis GM, Ferrari J, George P et al. 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. Lancet Neurology. 2016; 15(12):1238-47

47. Kim AS. Stroke risk prediction after transient ischaemic attack. Lancet Neurology. 2016; 15(12):1199-200

48. Kiyohara T, Kamouchi M, Kumai Y, Ninomiya T, Hata J, Yoshimura S et al. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. Stroke. 2014; 45(2):418-25

49. Knoflach M, Lang W, Seyfang L, Fertl E, Oberndorfer S, Daniel G et al. Predictive value of ABCD2 and ABCD3-I scores in TIA and minor stroke in the stroke unit setting. Neurology. 2016; 87(9):861-9

50. Lavallee PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurology. 2007; 6(11):953-60

51. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurology. 2015; 14(9):903-13

52. Merwick A, Albers GW, Amarenco P, Arsava EM, Ay H, Calvet D et al. Addition of brain and carotid imaging to the ABCD2 score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. Lancet Neurology. 2010; 9(11):1060-9

53. Merwick A, Albers GW, Arsava EM, Ay H, Calvet D, Coutts SB et al. Reduction in early stroke risk in carotid stenosis with transient ischemic attack associated with statin treatment. Stroke. 2013; 44(10):2814-20

54. Mlynash M, Olivot JM, Tong DC, Lansberg MG, Eyngorn I, Kemp S et al. Yield of combined perfusion and diffusion MR imaging in hemispheric TIA. Neurology. 2009; 72(13):1127-33

55. Mortezabeigi HR, Taghizadeh A, Talebi M, Amini K, Goldust M. ABCD2 score and BNP level in patients with TIA and cerebral stroke. Pakistan Journal of Biological Sciences. 2013; 16(21):1393-7

56. Munro S, Rodbard S, Ali K, Horsfield C, Knibb W, Holah J et al. A pilot study evaluating the use of ABCD2 score in pre-hospital assessment of patients with suspected transient ischaemic attack: experience and lessons learned. Experimental & Translational Stroke Medicine. 2016; 8:6

57. Nah HW, Kwon SU, Kang DW, Lee DH, Kim JS. Diagnostic and prognostic value of multimodal MRI in transient ischemic attack. International Journal of Stroke. 2014; 9(7):895-901

58. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available

from:
http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

59. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal 2013. London. National Institute for Health and Clinical Excellence, 2013. Available from: http://publications.nice.org.uk/pmg9

60. O'Brien EC, Zhao X, Fonarow GC, Schulte PJ, Dai D, Smith EE et al. Quality of care and ischemic stroke risk after hospitalization for transient ischemic attack: Findings from get with the guidelines-stroke. Circulation Cardiovascular Quality & Outcomes. 2015; 8(6 Suppl 3):S117-24

61. Ohara T, Uehara T, Toyoda K, Suzuki R, Sato S, Nagatsuka K et al. Early stroke risk after transient ischemic attack in patients without large-artery disease or atrial fibrillation. Journal of Stroke and Cerebrovascular Diseases. 2015; 24(7):1656-61

62. Ozpolat C, Denizbasi A, Akoglu H, Onur O, Eroglu SE, Demir H. Use of ABCD2 risk scoring system to determine the short-term stroke risk in patients presenting to emergency department with transient ischaemic attack. Journal of the Pakistan Medical Association. 2013; 63(9):1142-6

63. Ozturk M, Yuzbasioglu Y, Akinci E, Tanrikulu C, Kunt R, Coskun F. An evaluation of ABCD2 scores, atrial fibrillation, serum CRP, fibrinogen and D-dimer levels as diagnostic predictors for stroke in patients admitted to emergency department with the diagnosis of transient ischemic attack. Journal of Neurological Sciences. 2016; 33(3):473-81

64. Perry JJ, Losier JH, Stiell IG, Sharma M, Abdulaziz K. National survey of neurologists for transient ischemic attack risk stratification consensus and appropriate treatment for a given level of risks. Journal of Stroke and Cerebrovascular Diseases. 2015; 24(11):2514-20

65. Perry JJ, Sharma M, Sivilotti ML, Sutherland J, Symington C, Worster A et al. Prospective validation of the ABCD2 score for patients in the emergency department with transient ischemic attack. Canadian Medical Association Journal. 2011; 183(10):1137-45

66. Purroy F, Begue R, Quilez A, Pinol-Ripoll G, Sanahuja J, Brieva L et al. The California, ABCD, and Unified ABCD2 risk scores and the presence of acute ischemic lesions on diffusion-weighted imaging in TIA patients. Stroke. 2009; 40(6):2229-32

67. Purroy F, Jimenez-Caballero PE, Mauri-Capdevila G, Torres MJ, Gorospe A, Ramirez Moreno JM et al. Predictive value of brain and vascular imaging including intracranial vessels in transient ischaemic attack patients: external validation of the ABCD3-I score. European Journal of Neurology. 2013; 20(7):1088-93

68. Purroy F, Montaner J, Molina CA, Delgado P, Arenillas JF, Chacon P et al. C-reactive protein predicts further ischemic events in transient ischemic attack patients. Acta Neurologica Scandinavica. 2007; 115(1):60-6

69. Quinn TJ, Cameron AC, Dawson J, Lees KR, Walters MR. ABCD2 scores and prediction of noncerebrovascular diagnoses in an outpatient population: a case-control study. Stroke. 2009; 40(3):749-53

70. Ranta A, Dovey S, Weatherall M, O'Dea D, Tiyard M, Gommans J. Utility of ABCD2 score and expanded New Zealand TIA guideline criteria to predict 90-day stroke risk. International Journal of Stroke. 2015; 10(Suppl 3):4

71. Raser JM, Cucchiara BL. Modifications of the ABCD2 score do not improve the risk stratification of transient ischemic attack patients. Journal of Stroke and Cerebrovascular Diseases. 2012; 21(6):467-70

72. Robichaud L, Saluja SS. The ABCD2 score: A poor predictor of stroke risk in the emergency department. Canadian Journal of Emergency Medicine. 2014; 16(1):66-8

73. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet. 2007; 370(9596):1432-42

74. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet. 2005; 366(9479):29-36

75. Saedon M, Hutchinson CE, Imray CHE, Singer DRJ. ABCD^2 risk score does not predict the presence of cerebral microemboli in patients with hyper-acute symptomatic critical carotid artery stenosis. Stroke & Vascular Neurology. 2017; 2(2):41-6

76. Sciolla R, Melis F, Group S. Rapid identification of high-risk transient ischemic attacks: prospective validation of the ABCD score. Stroke. 2008; 39(2):297-302

77. Selvarajah JR, Smith CJ, Hulme S, Georgiou RF, Vail A, Tyrrell PJ et al. Prognosis in patients with transient ischaemic attack (TIA) and minor stroke attending TIA services in the North West of England: the NORTHSTAR Study. Journal of Neurology, Neurosurgery and Psychiatry. 2008; 79(1):38-43

78. Sheehan OC, Merwick A, Kelly LA, Hannon N, Marnane M, Kyne L et al. Diagnostic usefulness of the ABCD2 score to distinguish transient ischemic attack and minor ischemic stroke from noncerebrovascular events: the North Dublin TIA Study. Stroke. 2009; 40(11):3449-54

79. Song B, Fang H, Zhao L, Gao Y, Tan S, Lu J et al. Validation of the ABCD3-I score to predict stroke risk after transient ischemic attack. Stroke. 2013; 44(5):1244-8

80. Song B, Pei L, Fang H, Zhao L, Gao Y, Wang Y et al. Validation of the RRE-90 scale to predict stroke risk after transient symptoms with infarction: A prospective cohort study. PloS One. 2015; 10(9):e0137425

81. Sun W, Dai J, Xiong Y, Huang Z, Li Y, Liu W et al. Correlation between ABCD, ABCD2 scores and craniocervical artery stenosis in patients with transient ischemic attack. European Neurology. 2013; 70(5-6):333-9

82. Tsivgoulis G, Spengos K, Manta P, Karandreas N, Zambelis T, Zakopoulos N et al. Validation of the ABCD score in identifying individuals at high early risk of stroke after a transient ischemic attack: a hospital-based case series study. Stroke. 2006; 37(12):2892-7

83. Tsivgoulis G, Stamboulis E, Sharma VK, Heliopoulos I, Voumvourakis K, Teoh HL et al. Multicenter external validation of the ABCD2 score in triaging TIA patients. Neurology. 2010; 74(17):1351-7

84. Walker J, Isherwood J, Eveson D, Naylor AR. Triaging TIA/minor stroke patients using the ABCD2 score does not predict those with significant carotid disease. European Journal of Vascular and Endovascular Surgery. 2012; 43(5):495-8

85. Wang J, Wu J, Liu R, Gao F, Hu H, Yin X. The ABCD2 score is better for stroke risk prediction after anterior circulation TIA compared to posterior circulation TIA. International Journal of Neuroscience. 2015; 125(1):50-5

86. Wardlaw JM, Brazzelli M, Chappell FM, Miranda H, Shuler K, Sandercock PA et al. ABCD2 score and secondary stroke prevention: meta-analysis and effect per 1,000 patients triaged. Neurology. 2015; 85(4):373-80

87. Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. Health Technology Assessment. 2006; 10(30)

88. Yilmaz BK, Cevik E, Celik Y, Dogan H, Uzun O, Sayin T et al. A new scoring system predicting acute ischemic stroke: NIHSS+ABCD2. Acta Medica Mediterranea. 2014; 30(3):621-6

89. Yuan Z, Voss EA, DeFalco FJ, Pan G, Ryan PB, Yannicelli D et al. Risk prediction for ischemic stroke and transient ischemic attack in patients without atrial fibrillation: A retrospective cohort study. Journal of Stroke and Cerebrovascular Diseases. 2017; 26(8):1721-31

90. Zhang C, Wang Y, Zhao X, Liu L, Wang C, Pu Y et al. Prediction of recurrent stroke or transient ischemic attack after noncardiogenic posterior circulation ischemic stroke. Stroke. 2017; 48(7):1835-41

91. Zhang C, Zhao X, Wang C, Liu L, Ding Y, Akbary F et al. Prediction factors of recurrent ischemic events in one year after minor stroke. PloS One. 2015; 10(3):e0120105

92. Zhao M, Wang S, Zhang D, Zhang Y, Deng X, Zhao J. Comparison of stroke prediction accuracy of ABCD2 and ABCD3-I in patients with transient ischemic attack: A meta-analysis. Journal of Stroke and Cerebrovascular Diseases. 2017; 26(10):2387-95

1

1 Appendices

2 Appendix A: Review protocols

3 **Table 11: Review protocol: Risk prediction tools**

Field	Content
Review question	How accurately do scoring systems predict the risks of future ischaemic stroke or TIA within the first 7 days in people with suspected TIA or minor stroke?
Type of review question	Prognostic (clinical prediction rule) A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine if any risk prediction tools are useful in stratifying patients with TIA for risk of future stroke.
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with suspected TIA
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Validated risk stratification tools/scoring systems (ABCD2 and other variants e.g. ABCD2-I, ABCD3, ABCD3-I)
Eligibility criteria – comparator(s) / control or reference (gold) standard	Reference standard of confirmed stroke
Outcomes and prioritisation	Discrimination (area under curve [c statistic]) Calibration (R^2, Brier Score, Hosmer-Lemeshow test statistic; Somers' D statistic), Calibration plot Reclassification <u>These will be assessed for the following outcomes:</u> Critical Risk of stroke (stroke at 24 hours, 72 hours and 7 days) - area under curve (AUC). Mortality at 7 days Important Functional outcomes – mRS at 90 days and 1 year Quality of life Plan to report calibration and discrimination of tools
Eligibility criteria – study design	Prospective observational studies Systematic reviews and meta-analyses of the above Exclusions: derivation studies/internal validation studies
Other inclusion criteria	Inclusion Language: Restrict to English only Settings General practice, walk in centres, UCCs, pre-hospital setting (paramedic / ambulance), emergency department.

Field	Content
Proposed sensitivity / subgroup analysis, or meta-regression	None
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• EndNote will be used for reference management, sifting, citations and bibliographies. • Data extraction into word and quality assessment in excel using PROBAST checklist • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Medline, Embase, Cochrane Library, Cut-off date: 2007 Key papers 1. Giles MF and Rothwell PM. (2010) Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischemic attack risk scores. Stroke 41:667-673. 2. Wardlaw J, Brazzelli M, Miranda H et al. (20-6-2014) An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. Health Technology 3. Wardlaw J, Brazzelli M, Miranda H et al. (20-6-2014) An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. Health Technology Assessment (Winchester, England) 18:1-368.
Identify if an update	Yes, CG68 included 5 studies up to 2007. Recommendations from CG68 1.1.2.1 People who have had a suspected TIA (that is, they have no neurological symptoms at the time of assessment [within 24 hours]) should be assessed as soon as possible for their risk of subsequent stroke using a validated scoring system[9], such as ABCD2. [9]=These scoring systems exclude certain populations that may be at particularly high risk of stroke, such as those with recurrent TIAs and those on anticoagulation treatment, who also need urgent evaluation. They also may not be relevant to patients who present late.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all	For details please see evidence tables in Appendix D (clinical evidence

Field	Content
variables to be collected	tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies (PROBAST for clinical prediction rules). For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 12: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)

	• Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[58] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

	Health economic study type: • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

Searches were constructed using the following approach:

- Population AND Prognostic/risk factor terms AND Study filter(s)

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 12 January 2018	Exclusions Randomised controlled trials Systematic review studies Diagnostic tests studies
Embase (OVID)	1974 – 12 January 2018	Exclusions Randomised controlled trials Systematic review studies Diagnostic tests studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 1 of 12 CENTRAL to 2017 Issue 12 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Medline (Ovid) search terms

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	exp Brain Ischemia/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	Ischemic Attack, Transient/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	letter/

9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	Decision Support Techniques/
31.	Health Status Indicators/
32.	Severity of Illness Index/
33.	Triage/
34.	((risk* or predict* or prognos* or triage* or warning) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
35.	(predict* adj4 (outcome* or risk*)).ti,ab.
36.	((score* or scoring or stratif*) adj3 (system* or schem*)).ti,ab.
37.	or/30-36
38.	ABCD*.ti,ab.
39.	37 or 38
40.	predict.ti.
41.	(validat* or rule*).ti,ab.
42.	(predict* and (outcome* or risk* or model*)).ti,ab.
43.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
44.	decision*.ti,ab. and logistic models/
45.	(decision* and (model* or clinical*)).ti,ab.
46.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
47.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
48.	ROC curve/
49.	or/40-48

50.	randomized controlled trial.pt.
51.	controlled clinical trial.pt.
52.	randomi#ed.ti,ab.
53.	placebo.ab.
54.	randomly.ti,ab.
55.	Clinical Trials as topic.sh.
56.	trial.ti.
57.	or/50-56
58.	Meta-Analysis/
59.	Meta-Analysis as Topic/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	exp "sensitivity and specificity"/
70.	(sensitivity or specificity).ti,ab.
71.	((pre test or pretest or post test) adj probability).ti,ab.
72.	(predictive value* or PPV or NPV).ti,ab.
73.	likelihood ratio*.ti,ab.
74.	likelihood function/
75.	(ROC curve* or AUC).ti,ab.
76.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
77.	gold standard.ab.
78.	or/69-77
79.	29 and 39 and (49 or 57 or 68 or 78)

1 **Embase (Ovid) search terms**

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	*Transient ischemic attack/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.

10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
27.	25 not 26
28.	decision support system/
29.	health status indicator/
30.	"severity of illness index"/
31.	emergency health service/
32.	((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
33.	(predict* adj4 (outcome* or risk*)).ti,ab.
34.	((score* or scoring or stratif*) adj3 (system* or schem*)).ti,ab.
35.	or/28-34
36.	ABCD*.ti,ab.
37.	35 or 36
38.	predict.ti.
39.	(validat* or rule*).ti,ab.
40.	(predict* and (outcome* or risk* or model*)).ti,ab.
41.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
42.	decision*.ti,ab. and Statistical model/
43.	(decision* and (model* or clinical*)).ti,ab.
44.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
45.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
46.	Receiver operating characteristic/
47.	or/38-46
48.	random*.ti,ab.
49.	factorial*.ti,ab.
50.	(crossover* or cross over*).ti,ab.

51.	((doubl* or singl*) adj blind*).ti,ab.
52.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
53.	crossover procedure/
54.	single blind procedure/
55.	randomized controlled trial/
56.	double blind procedure/
57.	or/48-56
58.	systematic review/
59.	Meta-Analysis/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	exp "sensitivity and specificity"/
70.	(sensitivity or specificity).ti,ab.
71.	((pre test or pretest or post test) adj probability).ti,ab.
72.	(predictive value* or PPV or NPV).ti,ab.
73.	likelihood ratio*.ti,ab.
74.	((area under adj4 curve) or AUC).ti,ab.
75.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
76.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
77.	diagnostic accuracy/
78.	diagnostic test accuracy study/
79.	gold standard.ab.
80.	or/69-79
81.	27 and 37 and (47 or 57 or 68 or 80)

1 **Cochrane Library (Wiley) search terms**

2

#1.	(mini or minor or mild or acute) near/2 (stroke or strokes):ti,ab
#2.	MeSH descriptor: [Brain Ischemia] explode all trees
#3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#4.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#5.	(isch?emi* near/2 attack*):ti,ab
#6.	TIA*:ti,ab

#7.	(or #1-#6)
#8.	MeSH descriptor: [Decision Support Techniques] this term only
#9.	MeSH descriptor: [Health Status Indicators] this term only
#10.	MeSH descriptor: [Severity of Illness Index] this term only
#11.	MeSH descriptor: [Triage] this term only
#12.	((risk* or predict* or prognos* or triage* or warning) near/4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)):ti,ab
#13.	(predict* near/4 (outcome* or risk*)):ti,ab
#14.	((score* or scoring or stratif*) near/3 (system* or schem*)):ti,ab
#15.	(or #8-#14)
#16.	ABCD*.ti,ab.
#17.	(or #15-#16)
#18.	#7 and #17

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the stroke population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

B.2.1 Health economics search

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 – March 2015	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.

7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/
40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/

46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

1 **Embase (Ovid) search terms**

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.

24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(financ* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

1 NHS EED and HTA (CRD) search terms

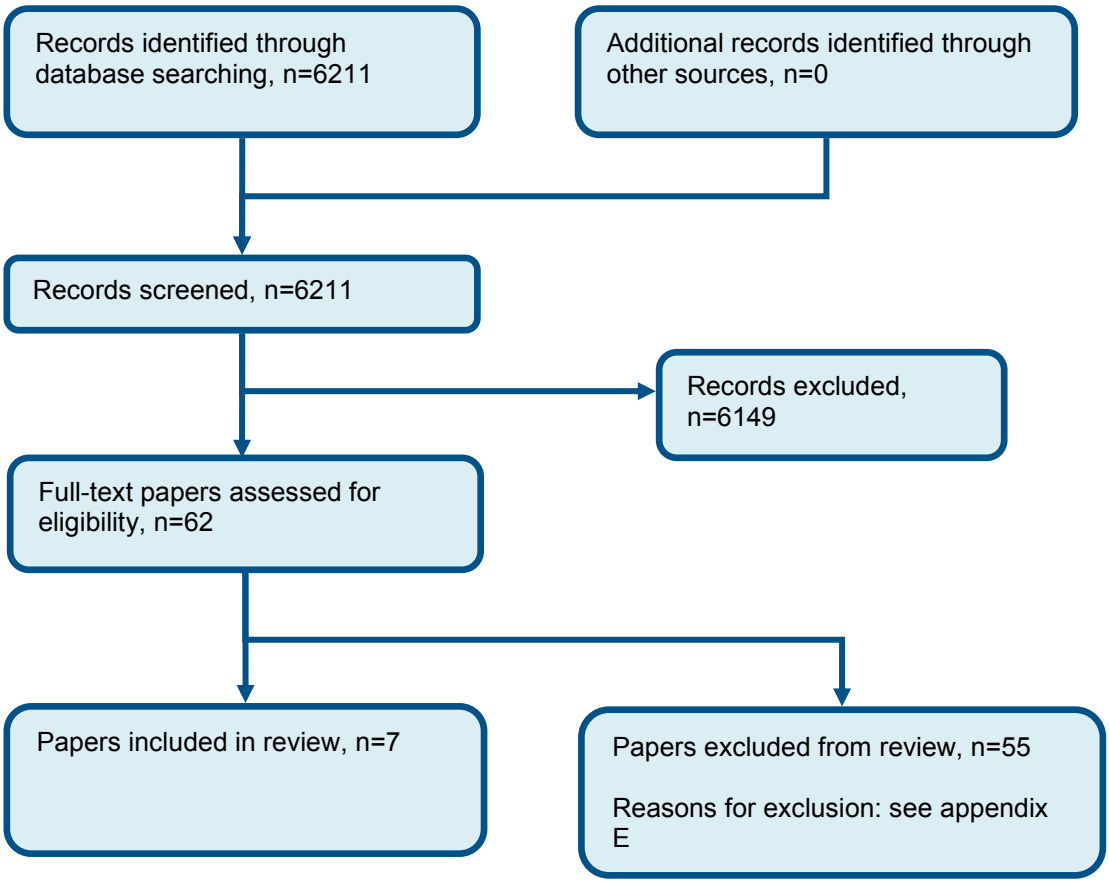
#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	(((cerebro* or cerebral*) adj2 (accident* or apoplexy)))
#4.	((CVA or poststroke or poststrokes))
#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	(((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)))

#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

1

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of risk prediction tools



Appendix D: Clinical evidence tables

Reference	Kelly 2015[46]
Study type and analysis	A pooled analysis of individual-patient data (IPD) 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. Literature search from Oct 2010 to Nov 2015, 19 studies identified, of which 12 groups agreed to participate. Five groups in Toulouse (France), Stanford (CA, USA), Athens (Greece), and Dublin and Oxford (UK) provided additional unpublished data. Data were abstracted from existing TIA registries at each centre using a standardised electronic template, locally de-identified, and collated centrally. All data (published and unpublished) were combined in a central database and coded with a centre identifier number or code. Teleconferences were arranged with participating centres to discuss data definitions if necessary. 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 fi le review. 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. Bivariate logistic regression was used to assess the association of vascular risk factors and variables included in the ABCD2 score with 7 day stroke (i.e., 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 (i.e., 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). 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. 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.
Number of participants and characteristics	n=2176 12 collaborative groups at 16 centres in Asia, Europe, and the USA Setting: All patients were assessed in hospital settings by stroke specialists, either as inpatients, in emergency departments, or in transient ischaemic attack clinics.

Reference	Kelly 2015[46]
	Inclusion: TIA confirmed by a stroke specialist, age >18 years, and brain MRI information available within 7 days of transient ischaemic attack onset and before stroke recurrence. Exclusion: Diagnosis other than TIA, individual first sought medical attention, had brain imaging for a stroke recurrence rather than the index TIA <u>Stroke recurrence in pooled analysis:</u> 2 days: Patients included versus patient excluded: 30/2085 (1%) versus 46/1326 (3%), p<0·001 7 days: Patients included versus patient excluded: 49/2108 (2%) versus 83/1327 (6%), p<0·001 Clinical characteristics in pooled analysis versus excluded patients (n/N (%) or median (IQR)) Men: Patients included versus patient excluded: 1274/2174 (59%) versus 714/1347 (53%), p=0.004 Age: Patients included versus patient excluded: 68 (57–77) vs 69 (59–78), p=0.01 Hypertension: Patients included versus patient excluded: 1459/2146 (68%) versus 890/1342 (66%), p=0.3 Atrial fibrillation: Patients included versus patient excluded: 272/2141 (13%) versus 204/1104 (18%), p <0·001 Dual TIA: Patients included versus patient excluded: 414/1980 (21%) versus 136/1114 (12%), p <0·001 Coronary artery disease: Patients included versus patient excluded: 270/1873 (14%) versus 238/1271 (19%), p <0·001 Carotid stenosis: Patients included versus patient excluded: 249/2082 (12%) versus 207/1303 (16%), p= 0·001 Diabetes: Patients included versus patient excluded: 361/2171 (17%) versus 253/1354 (19%), p=0.1 MRI done: Patients included versus patient excluded: 2176/2176 (100%) versus 250/782 (32%), p <0·001 ABCD2 score Patients included versus patient excluded: 4 (3–5) versus 4 (3–5), p=0·4

<table>
<tr><th>Reference</th><th>Kelly 2015[46]</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Risk tool</td><td>ABCD2, ABCD2-I, ABCD3-I</td></tr>
<tr><td>Outcomes and effect sizes</td><td>ABCD2 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).
Multivariable logistic regression
AUC (c statistic, 95% CI)
ABCD2
2 day stroke: 0·64 (0·56–0·71)
7 day stroke: 0·61 (0·53–0·67)

ABCD2-I
2 day stroke: 0·74 (0·67–0·80)
7 day stroke: 0·71 (0·64–0·77)

ABCD3-I
2 day stroke: 0·84 (0·76–0·90)
7 day stroke: 0·76 (0·69–0·83)

Risk of stroke
<table>
<tr><td></td><td colspan="2">2 day</td><td colspan="2">7 day</td></tr>
<tr><td></td><td>Events/non events</td><td>Percentage risk</td><td>Events/non events</td><td>Percentage risk</td></tr>
<tr><td>ABCD2 0 - 3</td><td>3/671</td><td>0.45%</td><td>7/680</td><td>1.03%</td></tr>
<tr><td>ABCD2 4 - 5</td><td>22/892</td><td>2.47%</td><td>32/902</td><td>3.55%</td></tr>
<tr><td>ABCD2 6 - 7</td><td>5/253</td><td>1.98%</td><td>9/253</td><td>3.56%</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>ABCD2-I 0 - 3</td><td>1/516</td><td>0.19%</td><td>3/516</td><td>0.58%</td></tr>
<tr><td>ABCD2-I 4 - 7</td><td>20/1039</td><td>1.92%</td><td>30/1054</td><td>2.85%</td></tr>
<tr><td>ABCD2-I 8 - 10</td><td>9/261</td><td>3.45%</td><td>15/265</td><td>5.66%</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>ABCD3-I 0 - 3</td><td>1/407</td><td>0.25%</td><td>2/408</td><td>0.49%</td></tr>
<tr><td>ABCD3-I 4 - 7</td><td>8/1108</td><td>0.72%</td><td>18/1126</td><td>1.60%</td></tr>
</table></td></tr>
</table>

Reference	Kelly 2015[46]

ABCD3-I 8 - 13	21/301	6.98%	28/301	9.30%

Calibration:
ABCD3-I χ^2 = 17.9 (well calibrated <20)
ABCD2-I χ^2 = 93.9 (poor calibration)

Comments	No included cohorts were used in the derivation of the ABCD3-I score. Some patients from Dublin and Oxford were included in the derivation of the ABCD2-I (validation cohort in Merwick et al). High/very high risk of bias: 7/19 eligible studies were unable or unwilling to provide IPD, this is a high rate of missing data Selection bias in excluding those who did not have imaging It is unclear how risk of bias was assessed and the methodological quality of the included studies is not reported. Methodological quality of the included studies is not reported

1

Reference	Merwick 2010[52]
Study type and analysis	Pooled international multicentre analysis of patients with TIA (IPD analysis). Studies identified by Medline (1950 to August, 2010) and Embase (1980 to August, 2010). Data were extracted from existing TIA registries at every centre with a standardised electronic template, de-identified, and collated at a central site. Stroke status at 2, 7, 28, and 90 days was recorded by in-person assessment, or telephone interview and medical file review, or both. Data from patients with periprocedural stroke after carotid revascularisation (endarterectomy or stenting) were excluded from analysis and were not obtained from participating centres. The information was assessed on recurrent TIA, carotid stenosis, and DWI abnormality in a step-wise fashion to generate the new versions of the ABCD² score. derivation of the extended scores, validation was done in an independent sample of patients. Multivariate logistic regression analysis was done with stroke as the dependent variable, with inclusion of independent clinical variables associated at the p<0·05 level on univariate analysis. On examining calibration of the ABCD³ and ABCD³-I scores in the validation sample, approximation of observed to predicted risk was limited across risk categories (χ^2 >20, p<0·01 for both scores).
Number of participants and characteristics	n=2654 in derivation cohort n= 1232 in validation cohort

Reference	Merwick 2010[52]
	Derivation cohort: 8 centres from Europe and North America (7 centres contributed data from patients admitted to hospital and 1 from patients who visited a 7-day TIA clinic that was run by a stroke specialist. Validation cohort: independent group of patients with TIA primarily participating in population-based studies in Oxfordshire, UK (from 2002-2009) and Dublin, Ireland (December 2005, to November 2008), and patients who attended hospital services (inpatient services and specialist clinics) run by stroke specialists or a daily TIA clinic from December 2008 to February 2010. Inclusion: TIA verified by a stroke specialist; and ABCD2 and carotid, ECG, or DWI information available within 7 days of TIA. Inclusion criteria for the validation sample were identical to those for the derivation sample except that patients who had brain imaging done with either DWI or CT for assessment of TIA within 28 days of the index attack were included. Exclusion: diagnosis other than TIA or if stroke occurred after carotid endarterectomy or stenting. Patients who first sought medical attention or had brain imaging for a stroke recurrence rather than the index TIA were excluded from analysis of the imaging-based score. Clinical characteristics of patients in pooled derivation sample (n/N(%) or mean (SD)) Men: 1467/2654 (55·3%) Age (years): 65·4 (15·0) Atrial fibrillation: 244/2654 (9·2%) History of stroke: 150/1725 (8·7%) Dual TIA: 483/2488 (19·4%) Coronary artery disease: 386/2559 (15·1%) Carotid stenosis: 227/1916 (11·8%) ABCD2 score 0–3: 1056/2611 (40·4%) 4–5: 1222/2611 (46·8%) 6–7: 333/2611 (12·8%) Time of diffusion-weighted imaging Within 24 h: 1104/2654 (41·6%) Within 72 h: 1571/2654 (59·2%)

Reference	Merwick 2010[52]
	Within 7 days: 1943/2654 (73·2%) Stroke recurrence 2 days: 27/2572 (1·0%) 7 days: 49/2576 (1·9%) 28 days: 56/1875 (3·0%) 90 days: 73/1877 (3·9%)
Prognostic variables	ABCD2, ABCD3, ABCD3-I
Outcomes and effect sizes	AUC (c statistic, 95% CI) Derivation cohort ABCD2 Day 2 stroke: 0·71 (0·62–0·77) Day 7 stroke: 0·71 (0·64–0·77) ABCD3 Day 2 stroke: 0·78 (0·69–0·86) Day 7 stroke: 0·80 (0·74–0·85) ABCD3-I Day 2 stroke: 0·90 (0·70–0·99) Day 7 stroke: 0·92 (0·79–0·99) Validation cohort ABCD2 Day 7 stroke: 0·63 (0·56–0·69) ABCD3 Day 7 stroke: 0·64 (0·58–0·71) ABCD3-I Day 7 stroke: 0·71 (0·63–0·78)

Reference	Merwick 2010[52]

Repeated analysis of discrimination without inclusion of CT data
ABCD3-I
Day 7 stroke: 0.72 (0.63-0.74)

Multivariate logistic regression model for stroke recurrence in derivation group
*Compared with lowest category (0–3)

2 days (n=2362; 24 had stroke recurrence)
ABCD2 (score 4–5)* OR: 9·12 (2·07–40·10)
ABCD2 (score 6–7)* OR:13·45 (2·66–67·99)
Dual transient ischaemic attack OR: 5·70 (2·52–12·90)

7 days (n=2366; 45 had stroke recurrence)
ABCD2 (score 4–5)* OR: 5·26 (2·14–12·92)
ABCD2 (score 6–7)* OR: 9·57 (3·49–26·24)
Dual transient ischaemic attack OR: 6·53 (3·56–11·98)

Risk of stroke at 7 days in validation cohort

ABCD2, 0 - 3	0.6%
ABCD2, 4 - 5	2.5%
ABCD2, 6 - 7	4.3%
ABCD3, 0 - 3	1.1%[(a)]
ABCD3, 4 - 5	2.5%[(a)]
ABCD3, 6 - 9	10.7%[(a)]
ABCD3-I, 0 - 3	0.9%[(a)]
ABCD3-I, 4 - 7	4.1%[(a)]

Reference	Merwick 2010[52]
	ABCD3-I, 8 - 13 | 9.8%(a) *(a) Data extracted from bar graph using WebPlotDigitizer online software* *Calibration:* *Derivation sample reported as well calibrated $\chi 2$ =10.92* *Validation sample ABCD3 and ABCD3-I, both reported as limited $\chi 2$ >20.*
Comments	High/very high risk of bias: Validation sample not systematically derived, patients not receiving imaging were excluded and insufficient info on risk of bias assessment

1

Reference	Asimos 2010 [6]
Study type and analysis	Prospective cohort study with non-consecutive enrolment from Stroke Registry hospitals Stroke status at 7 days was recorded by medical file review When ABCD2 scores were unavailable (35% of cohort) a multiple imputation strategy was used to estimate missing values.
Number of participants and characteristics	n=1667 Setting: 16 North Carolina Collaborative Stroke Registry hospitals enrolled over a 35 month period Inclusion: Presumptive diagnosis of TIA (sudden focal loss of neurologic function involving the brain or retina with complete recovery within 24 hours). Exclusion: History of stroke, unknown TIA symptom onset time, hospital presentation beyond 24 hours of TIA onset. Patient characteristics Mean (SD) age: 67.4 (15.1) years Previous TIA: 16.9% Atrial fibrillation: 10.4% Coronary artery disease: 22.5% Carotid stenosis: 2.8% Aspirin at admission: 36.5% Episode ≥60 minutes: 52.4%

Reference	Asimos 2010 [6]
	ABCD2 score 0–3: 13.9% 4–5: 33.6% 6–7: 15.9% Missing data: 36.8% Stroke occurrence 7 days: 373/1667 (22.4%)
Prognostic variables	ABCD2
Outcomes and effect sizes	AUC (C statistic, 95% CI) ABCD2 Day 7 stroke: 0.59 (0.56-0.62)
Comments	Outcome at high risk of bias due to the method of analysis, no other performance measures evaluated (for example, calibration or reclassification)

1

Reference	Tsivgoulis 2010 [83]
Study type and analysis	Prospective cohort study with consecutive enrolment from 3 tertiary care neurology hospitals Stroke status at 7 days was recorded by evaluating hospital records, physicians' notes, necropsy findings or death certificates. Follow-up evaluation was done by blinded assessors.
Number of participants and characteristics	n=148 Setting: 3 tertiary care neurology departments Inclusion: TIA patients hospitalised and diagnosed according to the WHO criteria. Exclusion: not stated Patient characteristics

Reference	Tsivgoulis 2010 [83]
	Mean (SD) age: 60 (14) years Coronary artery disease: 20% Atrial fibrillation: 14% Antiplatelets before hospitalisation: 39% All had extracranial Doppler/duplex ultrasonography, but MRI, MRA or ECG only in selected cases Stroke occurrence (defined as cerebrovascular events of sudden onset, lasting >24h, clearly resulting in an increase of existing or a new neurological deficit). 7 days: 12/148 (8.1%)
Prognostic variables	ABCD2
Outcomes and effect sizes	AUC (C statistic, 95% CI) ABCD2 Day 7 stroke: 0.72 (0.57-0.88)
Comments	Outcome at very high risk of bias due to the method of analysis, no other performance measures evaluated (for example, calibration or reclassification); and sample size, few events per predictor

1

Reference	Perry 2011 [65]
Study type and analysis	Prospective cohort study from 8 Canadian emergency departments 2007-2010. Stroke status at 7 days was recorded using hospital records from each site, including admission, clinic and autopsy reports. Follow-up evaluation was done by telephone with positive outcomes confirmed independently by blinded assessors.
Number of participants and characteristics	n=2056 (228 [11%] with minor stroke, not TIA) Setting: 8 Canadian emergency departments Inclusion: 18 years of age or older, final diagnosis of transient ischemic attack or minor stroke at the emergency department Exclusion: stroke confirmed at the time of assessment (i.e., neurologic deficit > 24 h), score <15 on the Glasgow Coma Scale, documented alternative cause for their deficit (e.g., hypoglycaemia, seizure, electrolyte imbalance or migraine) or presenting to the emergency department more than 7 days after their symptoms began.

Reference	Perry 2011 [65]
	Patient characteristics Mean (SD) age: 68.0 (14.3) Antihypertensives before hospitalisation: 50% Stroke occurrence 7 days: 38 (1.8%)
Prognostic variables	ABCD2
Outcomes and effect sizes	AUC (C statistic, 95% CI) ABCD2 calculated by enrolling physician Day 7 stroke: 0.56 (0.47-0.65) ABCD2 calculated by co-ordinating centre Day 7 stroke: 0.65 (0.58-0.73)
Comments	Outcome at very high risk of bias due to the method of analysis, no other performance measures evaluated (for example, calibration or reclassification); and sample size, few events per predictor

1

2

Reference	Ghandehari 2012 [33]
Study type and analysis	Prospective cohort study with consecutive enrolment from an Iranian hospital 2010-2011. Stroke status at 3 and 90 days was recorded directly at patient visit or by centralised telephone interview if patients failed to attend the visit.
Number of participants and characteristics	n=393 with TIA Setting: Hospital/stroke clinic Inclusion: Consecutive TIA or minor ischaemic stroke patients diagnosed by a neurologist, presenting within 24 hours from symptom onset and a pre-morbid mRS of ≤1.

Reference	Ghandehari 2012 [33]
	Exclusion: clinical evaluation beyond 24 hours from end of transient event, final diagnosis of non-ischaemic causes of symptoms; known cognitive impairment, disabling stroke (NIHSS ≥4 at 1 day after event) Patient characteristics Mean (SD) age: 68.5 (4.7) Stroke occurrence at 3 days: 132/393 (34%)
Prognostic variables	ABCD2
Outcomes and effect sizes	AUC (C statistic, 95% CI) ABCD2 Day 3 stroke: 0.591 (0.526-0.657) Vascular death at 3 days: 2 (0.5%) Vascular death at 3 months: 5 (1.3%)
Comments	Outcome at high risk of bias due to the method of analysis, no other performance measures evaluated (for example, calibration or reclassification)

1

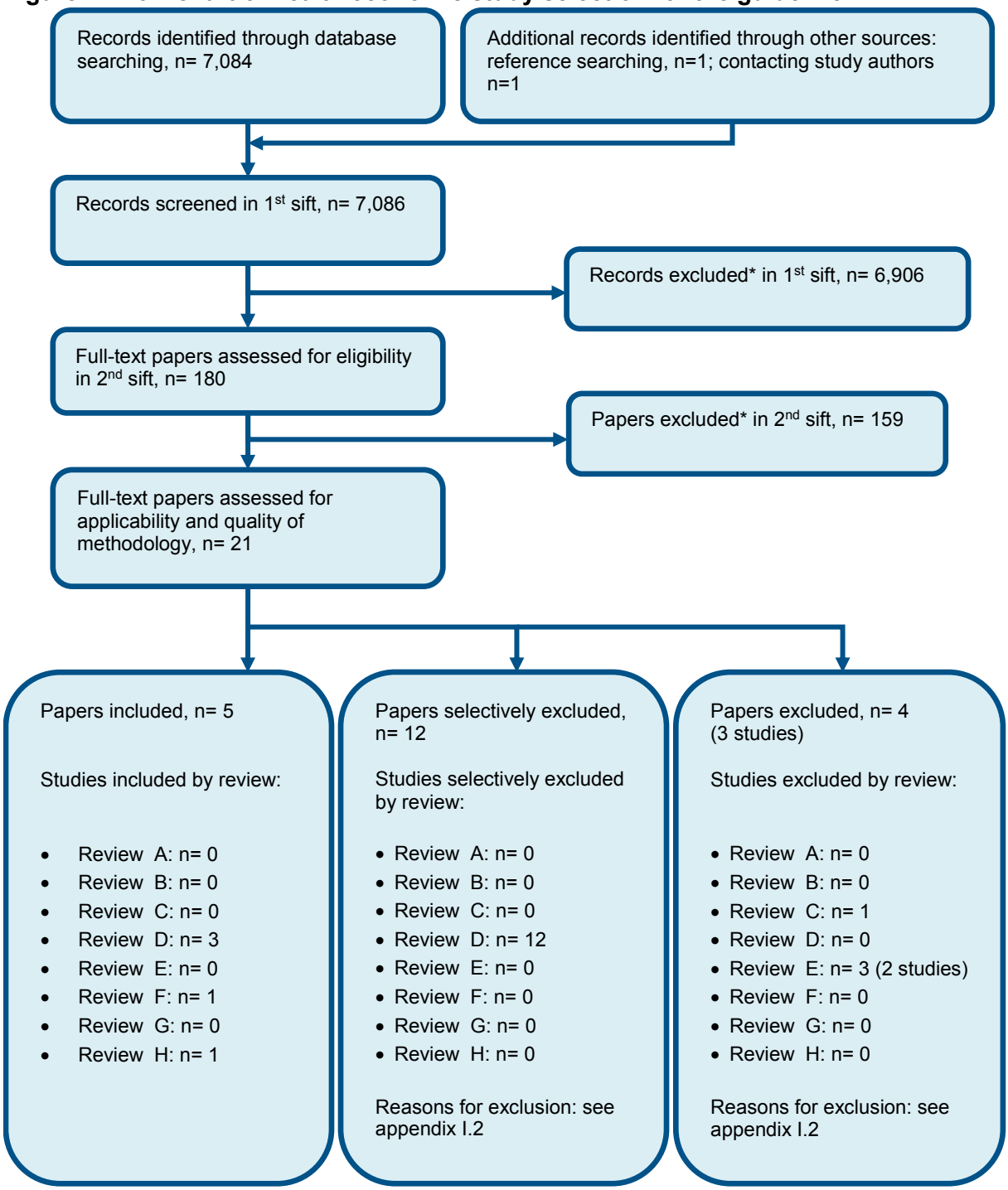
2

Reference	Ozpolat 2013 [62]
Study type and analysis	Prospective cohort study with consecutive enrolment from a Turkish ED in 2010. Stroke status at 3 days was recorded directly at patient visit or by centralised telephone interview.
Number of participants and characteristics	n=64 Setting: enrolled from ED Inclusion: age >18 years and had sufficient clinical suspicion to justify diagnostic testing for a neurovascular cause Exclusion: age <18, diagnosis of any kind of haemorrhage, a CT scan or other investigation that revealed a primary cause of the

Reference	Ozpolat 2013 [62]
	symptoms other than TIA, lack of informed consent, lack of specification of time of symptom onset or a clinical diagnosis of stroke Patient characteristics Mean (SD) age: 68.4 (11.79) years Previous TIA: 17.2% Atrial fibrillation: 15.6% Coronary artery disease: 23.4% History of stroke: 12.5% Stroke occurrence (defined as a rapidly developed focal or global disturbance of cerebral function, with no apparent non-vascular cause, lasting more than 24 hours or until death, and distinguishable from the event leading to the initial TIA diagnosis at 3 days: 8/64 (12.6%)
Prognostic variables	ABCD2
Outcomes and effect sizes	AUC (C statistic, 95% CI) ABCD2 Day 3 stroke: 0.76 (0.64-0.86)
Comments	Outcome at very high risk of bias due to the method of analysis, no other performance measures evaluated (for example, calibration or reclassification); and sample size, few events per predictor

Appendix E: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

1

2

3

4

Appendix F:Health economic evidence tables

Study	National Clinical Guideline for Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA) (CG68): https://www.nice.org.uk/guidance/cg68/evidence/full-guideline-pdf-196845517			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision tree model **Approach to analysis:** A decision tree was used to assess the cost effectiveness of each strategy for all people, irrespective of risk, and also broken down into subgroups of high risk and low risk using the ABCD^2 scoring system. The decision tree models the effect of the treatment strategies on incidence of stroke, and then divides by the type of stroke: fatal, dependent and independent. Costs and QALYs are then estimated for these groups and for people who do not experience a	**Population:** Suspected TIA/minor stroke **Cohort settings:** Start age: NR Male: NR **Intervention 1:** People with suspected TIA assessed within 7 days at a weekly specialist stroke unit clinic **Intervention 2:** People with suspected TIA assessed immediately, at a stroke unit	**Total costs (mean per patient):** Intervention 1: £6,199 Intervention 2: £6,104 Intervention 3: £5,430 Incremental (2−1): Saves £95 (95% CI: NR; p=NR) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** GP assessment: two consultations in the first month after TIA/minor stroke. Assessment at a stroke unit: staffing, overhead	**QALYs (mean per patient):** Intervention 1: 7.06 Intervention 2: 7.12 Intervention 3: 6.92 Incremental (2−1): 0.06 (95% CI: NR; p=NR)	**ICERs (all people with suspected TIA/minor stroke)** **ICER (Intervention 1 versus Intervention 3):** £5,412 (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **ICER (Intervention 2 versus Intervention 3):** £3,332(pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **ICER (Intervention 2 versus Intervention 1):** Dominant (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **Cost effectiveness by ABCD^2 score group** **Optimal strategy at £20,000 per QALY gained threshold:** ABCD^2 score 0-1: Intervention 3 ABCD^2 score 2-7: Intervention 2 **Analysis of uncertainty:** Costs of immediate and weekly assessment were varied in a probabilistic sensitivity analysis. Several one way sensitivity analyses were performed on key parameters such as costs and probability of stroke. The results were robust across the sensitivity analyses. The impact of including TIA mimics in the analysis was explored by doubling the cost of initial assessment in each strategy, to reflect a ratio of 1:1 of patients with actual TIA or minor stroke,

stroke. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 90 days **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 3:** Assessment by a GP (no specialist assessment)	costs, imaging and labs. Drug costs. Surgery costs. Costs of stroke care by stroke severity (dependent and independent)		to those with stroke mimics who are discharged without further treatment for stroke prevention. Immediate assessment remained the optimal strategy, with an ICER of £264 per QALY gained. The timing of endarterectomy was explored in a sensitivity analysis. For immediate assessment, 50% to 100% of surgery would take place within 2 weeks of TIA. For assessment at a weekly clinic, 0 to 50% of surgery would take place within 2 weeks of TIA.

Data sources

Health outcomes: The 2, 7 and 90 day incidences of stroke after TIA was from a published study which pooled 6 cohorts in England and USA (n=4799). People with lower ABCD^2 scores and stenosis level have lower baseline risk of stroke. The effectiveness of medical treatment was based on the Wardlaw HTA on carotid stenosis in the UK. [87] As the baseline data already account for aspirin use, the treatment effect used is a 15% reduction in the 90-day stroke risk for patients being assessed by specialists due to prescribing of modified release dipyridamole. Patients going immediately to the specialist clinic get this benefit from day 1, whereas patients being sent to the weekly clinic are assumed to get this effect from day 4. Patients not assessed by a specialist are less likely to be given appropriate medication and so have fewer strokes averted. Outcomes of strokes (fatal, dependent, and independent) were taken from the EXPRESS study. The life expectancy was derived from data for the general population in England & Wales from the Office for National Statistics for 2003–2005 and assumptions were made about life expectancies by stroke severity (dependent and independent). **Quality-of-life weights:** EQ-5D UK tariff. Utilities were obtained from the Wardlaw HTA. [87] **Cost sources:** The cost of assessment at a stroke unit was taken from costs for a one-stop TIA clinic. A range of costs were collected from various centres in the UK. The highest cost reported was used for immediate assessment (£410) and the mean cost was used for a weekly clinic (£316). A cost of £25 per 10 minute consultation was applied for GP assessment. Drug costs were from the BNF.

Comments

Source of funding: The National Institute for Health and Care Excellence. **Limitations:** The base case for the model assumes that all people with suspected TIA have a TIA or a minor stroke and so the costs and QALYs associated with TIA mimics are not captured. However, this was explored in a sensitivity analysis. The model is a simple representation, looking at only 90 days after the TIA for the effects of medical treatment and extrapolating from this to get long-term outcomes. **Other:** A carotid ultrasound scan was assumed to occur at the stroke unit. The sensitivities and specificities were from the Wardlaw HTA. [87] If the carotid scan is negative (carotid stenosis <50%), patients receive medical treatment alone. If the scan is positive (carotid stenosis ≥50%), patients receive surgery (endarterectomy) in addition to medical treatment. 6% of people were assumed to have a stenosis level of 70-99%, and 4% to have a level of 50-69% based on the Wardlaw HTA. [87] The Wardlaw HTA reported a 0.53% relative risk of stroke in patients with stenosis level <70% compared to ≥70%. In the base case analysis, it was assumed that 80% of patients who were assessed immediately and had a stenosis level of ≥50% would have surgery within 2 weeks of their TIA. For patients having specialist assessment at a weekly clinic, only 25% were assumed to have surgery within 2 weeks. All other patients with a stenosis level of ≥50% would have surgery from 2 to 4 weeks after their TIA.

Overall applicability: Directly applicable[(c)] **Overall quality:** Minor limitations[(d)]

Abbreviations: 95% CI: 95% confidence interval; BNF: British National Formulary; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GP: General Practitioner; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; TIA: transient ischaemic attack

(a) To extrapolate the treatment effect to the lifetime time horizon, a 25% reduction in stroke risk between 3-6 months was assumed for those taking aspirin and modified-release dipyridamole, from 6-12months, a reduction in stroke risk of 47% was assumed for those taking aspirin, modified-release dipyridamole and blood pressure-lowering drugs. From 1 year onwards, a risk reduction of 55% was assumed attributable to aspirin, modified-release dipyridamole, blood-pressure lowering drugs and lipid-lowering drugs.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix G: Excluded studies

G.1 Excluded clinical studies

Table 15: Studies excluded from the clinical review

Reference	Reason for exclusion
Almasi 2016[2]	Incorrect study type: Retrospective
Amarenco 2009[3]	No relevant outcomes
Amarenco 2016[4]	Incorrect follow up time
Appelros 2017[5]	Incorrect study type: Retrospective
Bejot 2016[8]	Incorrect study type: Narrative review
Bibok 2017[9]	No relevant outcomes
Cadth 2014[12]	Incorrect study type: Review
Chandratheva 2010[13]	Analysis of OXVASC data already included
Chandratheva 2011[14]	No relevant outcomes
Chardoli 2016[15]	Incorrect follow up time
Chardoli 2013[16]	No relevant outcomes
Chu 2015[18]	Systematic review: insufficient quality assessment of included studies
Cocho 2016[20]	Incorrect follow up time
Coutts 2015[21]	Incorrect study type: Review
Cutting 2016[24]	Incorrect study type: Retrospective
Dai 2015[26]	Incorrect follow up time
Duca 2016[28]	Incorrect study type: Review
Engelter 2012[29]	Incorrect follow up time
Fothergill 2009[31]	Incorrect study type: Retrospective
Ghandehari 2012[34]	Incorrect population
Ghia 2012[35]	Incorrect study type: Retrospective
Giles 2011[36]	Incorrect study type - meta-analysis
Giles 2010[37]	Incorrect study type - meta-analysis
Hotter 2012[38]	No relevant outcomes/incorrect intervention

Reference	Reason for exclusion
Ishida 2015[39]	Incorrect intervention
Jeerakathil 2014[40]	Not full study (protocol only)
Johansson 2014[41]	Incorrect study type: Retrospective cohort
Josephson 2008[44]	Incorrect study type: Retrospective cohort
Josephson 2008[43]	Incorrect intervention
Kim 2016[47]	Incorrect study type (comment)
Kiyohara 2014[48]	Incorrect study type: Retrospective cohort
Knoflach 2016[49]	No relevant outcomes
Mortezabeigi 2013[55]	Incorrect follow up time
Munro 2016[56]	Incorrect study design
O'Brien 2015[60]	Incorrect study design - Pilot study, includes retrospective data
Ohara 2015[61]	No relevant intervention
Ozturk 2016[63]	Incorrect follow up time
Perry 2015[64]	Incorrect study type: survey
Quinn 2009[69]	Incorrect outcome: AUC for prediction of non CV event
Ranta 2015[70]	Incorrect study type (conference abstract)
Raser 2012[71]	No relevant outcomes
Robichaud 2014[72]	No relevant outcomes
Saedon 2017[75]	Incorrect follow up time
Sciolla 2008[76]	Incorrect tool: ABCD scale
Selvarajah 2008[77]	Incorrect follow up time
Song 2015[80]	Incorrect follow up time
Sun 2013[81]	No relevant outcomes
Walker 2012[84]	No relevant outcomes
Wang 2015[85]	No relevant outcomes
Wardlaw 2015[86]	Incorrect study type - meta-analysis
Yilmaz 2014[88]	Incorrect intervention
Yuan 2017[89]	Incorrect study type: Retrospective cohort
Zhang 2017[90]	Incorrect intervention
Zhang 2015[91]	Incorrect intervention

Reference	Reason for exclusion
Zhao 2017[92]	Incorrect study type - meta-analysis