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Prognostic value of the ABCD2 clinical prediction rule: a systematic review and meta-analysis

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Prognostic value of the ABCD^2 clinical prediction rule: a systematic review and meta-analysis

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Abstract

Purpose: The $ABCD^2$ clinical prediction rule (CPR) is designed to predict early risk of stroke after transient ischaemic attack (TIA). The purpose of this systematic review with meta-analysis is to determine the predictive value of the $ABCD^2$ at 7 and 90 days across three strata of risk.

Methods: A systematic literature search was conducted to identify studies that validated the $ABCD^2$. The derived rule was used as a predictive model and applied to subsequent validation studies. Comparisons were made between observed and predicted number of strokes stratified by risk group, low (0-3 points), moderate (4-5 points) and high (6-7 points). Pooled results are presented as risk ratios (RRs) with 95% confidence intervals, in terms of over-prediction (RR>1) or under-prediction (RR<1) of stroke at 7 and 90 days.

Results: We include 16 validation studies. Fourteen studies report 7 day stroke risk (n=6282, 388 strokes). The $ABCD^2$ rule correctly predicts occurrence of stroke at 7 days across all three risk strata: low, (RR 0.86, 95%CI(0.47-1.58), I^2=16%); moderate, (RR 0.99, 95%CI(0.67-1.47), I^2=68%); high, (RR 0.84, 95%CI(0.6-1.19), I^2=46%). Eleven studies report 90 day stroke risk (n=6304). There is a non-significant trend towards over prediction of stroke in all risk categories at 90 days. There are 426 strokes observed in contrast to a predicted 626 strokes. As the trichotomised $ABCD^2$ score increases, the risk of stroke increases (p<0.01). There is no evidence of publication bias in these studies (p>0.05).

Conclusion: The $ABCD^2$ is a useful CPR, particularly in relation to 7 day risk of stroke.

Keywords: stroke, TIA, transient ischaemic attack, risk prediction, $ABCD^2$

Introduction

The incidence of transient ischaemic attack (TIA) in the United States is estimated to be in the region of 200,000-500,000 per year.[1] TIA and thrombotic stroke arise from identical aetiologies and a number of studies show that TIAs carry a significant risk of stroke.[2-4] The burden of stroke lies with its long term disability, therefore prevention of stroke in individuals with TIA could significantly reduce the overall incidence and burden of stroke. Many patients with TIA do not receive timely assessment or management and the challenge to clinicians is to identify those who require urgent evaluation and treatment. Two clinical prediction rules, the ABCD system and the California rule,[5-6] were developed to assist clinicians to quantify the short term risk of stroke after TIA. In 2007, these scores were unified and refined to form the $ABCD^2$ rule.[7]

The $ABCD^2$ system is designed to assist clinicians with the timely and appropriate management of individuals with TIA and also to target secondary prevention and inform public education.[8] The $ABCD^2$ rule is a 7 point summation of clinical factors independently predictive of stroke risk. These factors include age, clinical features such as motor impairments and speech disturbance, duration of symptoms, history of diabetes and hypertension. A summary of the rule is contained in Figure 1. The developers originally identified three strata of stroke risk after TIA according to $ABCD^2$ score; low (0-3 points), moderate (4-5 points) and high (6-7 points).[7] The $ABCD^2$ rule has been recommended for use in several national guidelines and management strategies based on the different guidelines are contained in Table 1.[9-12]

A number of studies have validated the $ABCD^2$ rule in different populations and recent systematic review reported that the overall 7 day predictive value of the $ABCD^2$ rule was high, resulting in predictive values ranging from 0.63 to 0.80 as the area under the receiver operating characteristic (ROC) curve at 7 days.[8] However, CPRs are designed to be applied in a clinically meaningful way in terms of assisting clinicians with correct diagnosis and management of patients. The aim of this study is to examine the predictive value of the $ABCD^2$ rule at 7 and 90 days using the original derivation study as a predictive model against which all subsequent validation studies are compared across three strata of risk, low (0-3 points), moderate (4-5 points) and high (6-7 points). Therefore, the absolute risk of stroke is presented in three risk strata so that the value of the $ABCD^2$ can be interpreted by clinicians. Our study aims to provide added clinical value to the findings of the previous review by presenting the results as trichotomised risk scores and not an aggregate measurement as with the ROC curve. We also examine internal and external sources of bias in the studies, including publication bias.

INCLUDE TABLE 1 AND FIGURE 1 HERE

Methods

Search strategy

The PRISMA guidelines for the reporting of systematic reviews and meta-analyses were followed to conduct this review.[13] We aimed to identify all studies of that validated the $ABCD^2$ rule irrespective of setting or study design. A literature search was conducted in July 2010 and included the following search engines: the Cochrane Library, EMBASE, Science Direct and PubMed. The databases were searched using a combination of the following keywords and MeSH terms: 'transient ischaemic attack' OR 'TIA' AND 'cerebrovascular accident' OR 'CVA' OR 'stroke' AND 'score' OR 'prediction' OR 'prognosis' OR 'risk'. The search was supplemented by hand searching references of retrieved articles and searching Google Scholar. No restrictions were placed on language.

Study selection and data extraction

Studies were included if they met the following inclusion criteria; 1) Study design: prospective or retrospective cohort studies; 2) Patient population: adult patients (>18 years of age) with a diagnosis of TIA - TIA is defined as a sudden focal neurologic deficit lasting for less than 24 hours, of presumed vascular origin, and confined to an area of the brain or eye perfused by a specific artery;[14] 3) Explanatory variables: $ABCD^2$ score calculated; 4) Setting of care: population and hospital based patients; and 5) Outcome measure: subsequent stroke at 7 or 90 days. The World Health Organization (WHO) define stroke as a clinical syndrome consisting of 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin'.[15] Studies that included patients with minor stroke, where symptoms lasted more than 24 hours, were excluded from the analysis. Studies

that included the same data set for more than one publication were included once in the meta-analysis. Two reviewers (RG and CG) read the titles and/or abstracts of the identified references and eliminated irrelevant studies. Studies that were considered eligible for inclusion were read fully in duplicate and their suitability for inclusion to the study was independently determined by both CG and RG. Disagreements were managed by consensus. Additional data was sought from authors where necessary. Data was extracted on study design and setting, patient characteristics, method of data extraction and outcome at the follow-up time points.

Validity Assessment

Quality assessment was independently performed by two researchers (RG and CG) following the modified methodological standards of McGinn for validation studies of CPRs.[16] The McGinn criteria examine the internal and external validity of studies in terms blinded assessment of predictor variables and outcome (stroke/no stroke), numbers followed up in the study (minimum ≥80%), methods of patient selection and spectrum of patients included with TIA.

Statistical Methods

The initial derivation study of the $ABCD^2$ rule is used as a predictive model against which subsequent validation studies are compared. The results are presented in a clinically meaningful way across three different strata of risk. The number of strokes predicted across the three strata of risk - low risk (score 0-3), moderate risk (score 4-5) and high risk (score 6-7) is compared with the observed number of strokes in each of the subsequent validation studies. Therefore the predicted number of patients with stroke at 7 and 90 days (based on

the probability calculated in the derivation study) is compared with the observed number of patients with stroke from each validation study. A sample of this calculation is contained in Table 2. A Chi-squared test for trend is computed to determine if there is an increasing trend in risk of stroke across the three $ABCD^2$ risk categories. In addition, a 2x2 table is used to calculate sensitivities and specificities at the different dichotomised cut points of ≥3, ≥4 and ≥5, as recommended in the national clinical guidelines (Table 1). We also examine the presence and extent of study effects or publication bias in the meta-analysis through the inspection of funnel plots.

INSERT TABLE 2 HERE

Review Manager 5 software from the Cochrane collaboration is used to perform the analysis, determine heterogeneity and produce forest plots. Results are presented as risk ratios (RR) with 95% confidence intervals using the Mantel-Haenszel statistical method. A RR score of 1 represents accurate prediction by the $ABCD^2$ rule, <1 represents under-prediction and >1 over-prediction. A random effects analysis was applied and heterogeneity across the studies was quantified using the I^2 statistic. If the I^2 statistic was >50%, it was deemed that there was significant heterogeneity between the studies.

Results

Study identification

A flow diagram of the search strategy is presented in Figure 2. Two researchers screened all potential articles. The search strategy yielded 2481 papers of which 2425 publications were excluded based on their title or abstract. Sixteen of the remaining 56 studies met the inclusion criteria and were selected for analysis.[7, 17-28]

Study description

Table 3 summarises the characteristics of the included studies. Four cohorts are published by Oxford or California researchers.[7] All publications are in English. Additional data was provided from six authors and clarification on methods of recruitment was sought from three authors. Four studies collected the ABCD^2 data prospectively,[20, 21, 23, 27] and twelve studies obtained the relevant information from patient notes retrospectively.[7, 17-19, 22, 24-26, 28] Eight studies were conducted in an Emergency Department,[7, 17, 20, 23-27] three were TIA-clinic based,[7, 28] two were population based,[7, 22] and three were based in specialty stroke centres.[18, 19, 21] The included studies range in size from 87,[20] to 1411 patients.[25] A total of 8482 participants are included in the analysis.

INSERT FIGURE 2 AND TABLE 3 HERE

Study quality

The methodological quality of the studies is detailed in Table 4. The external validity of the studies is good and the main shortcoming in relation to internal validity is with inadequate reporting of blinding in the included studies. There is no evidence of publication bias in the

studies included in the 7 day or 90 day analysis (p>0.05). See supplementary Appendices 1 and 2 respectively.

INSEERT TABLE 4 HERE

7 day stroke risk

Fourteen studies (n=6282) report 7 day risk of stroke.[7, 17-24, 26, 27] The $ABCD^2$ rule correctly predicts occurrence of stroke at 7 days across all three risk strata: low risk (n=2153), moderate risk (n=2943) and high risk (n=1186). The results are displayed in Figure 3. There are 357 strokes predicted and 388 strokes observed at 7 days across all three risk strata. A subgroup analysis of the two population based studies[7, 22] including patients recruited from primary care settings indicates that the ABCD2 rule performs well on the low and moderate risk groups but significantly under predicts the risk of stroke at 7 days in the high risk group (RR 0.48, 95% CI (0.27-0.88), I^2=0%).

The chi-squared analysis indicates that as the trichotomised $ABCD^2$ score increases, the probability of stroke increases (p<0.01). The sensitivity and specificity of the dichotomised cut points used to discriminate individuals at low and high risk of stroke at 7 days, which have been utilised in different national clinical guidelines, are contained in Table 5. Our pooled data indicates that 9.5% of the total strokes at 7 days occur in the low risk group, 51% are observed in the moderate risk group and 39.5% of the total strokes occur in the high risk group.

INSERT TABLE 5 HERE

90 day stroke risk

Eleven studies (n=6304) report 90 day risk of stroke.[7, 19-21, 25-28] The $ABCD^2$ rule tends to over predict the occurrence of stroke across all three risk strata: low risk (n=2205), moderate risk (n=2869) and high risk (n=1230). The results are presented in Figure 4. There are 426 strokes observed at 90 days in contrast to a predicted 626 strokes. The chi-squared analysis shows that as the trichotomised $ABCD^2$ score increases, the risk of stroke increases ($p<0.01$).The sensitivity and specificity of the cut points used to discriminate individuals at low and high risk of stroke at 90 days are contained in Table 5. At 90 days, 13.6% of all strokes observed occur in the low risk group, 50% occur in the moderate risk group and 36.4% occur in the high risk group.

INSERT FIGURES 3 AND 4 HERE

Discussion

Statement of principal findings

This systematic review shows that the $ABCD^2$ clinical prediction rule correctly predicts the occurrence of stroke at 7 days in individuals with TIA across all three strata of risk. However, a subgroup analysis of the population based studies indicates that the rule significantly under predicts the risk of stroke in those classified as high risk. At 90 days, the $ABCD^2$ rule tends to over-predict occurrence of stroke in the three risk categories. These results also show that the likelihood of having a stroke increases as the $ABCD^2$ trichotomised score increases.

Current context and future research directions

A recent systematic review examines the discriminative ability of the ABCD system using summary ROC curves.[8] Our method of calibration examines the predictive ability of the rule by using the ratio of predicted stroke (from the original derivation study) to observed stroke in the subsequent validation studies. The absolute risk of stroke is presented in risk strata so that the value of the $ABCD^2$ across these strata can be interpreted in a clinically meaningful way. The method of analysis used to pool the individual $ABCD^2$ validation studies is based on a comparative approach that extends and employs the absolute risk from the derivation study as a model to generate predicted values in subsequent validation studies. This statistical method is supported by an analysis that compares our method to a validated and published method for comparing predicted to observed values.[29] No statistically significant difference ($p>0.05$) was found between the predicted events by the two methods (unpublished study).

Our results support the findings of the previous review, suggesting that the $ABCD^2$ rule is a good predictor of stroke at 7 days and had been broadly validated in a wide variety of clinical settings. However, these is a need for future large multi-centre randomised controlled trials to examine the impact of applying the rule in different clinical settings, particularly in the primary care setting, in terms of patient outcome, clinician behaviour, cost effectiveness and resource use, or any combination of these.[30]

Strengths and weaknesses of the study

Our systematic review pools data from 16 separate cohorts of individuals with TIA. This facilitates an assessment of the performance of the $ABCD^2$ rule across different clinical settings, addressing validity, applicability and precision of estimates across three different strata of risk. Sixteen $ABCD^2$ validation studies are included in the previous review.[8] Five of these studies pertain to unpublished data that is not included in our review. However, we include data on five additional studies.[23, 25-28] We assess the predictive value of the $ABCD^2$ score at 7 and 90 days. Some authors have validated the $ABCD^2$ score at 2 days,[7, 23, 26] and it is widely accepted that the risk of stroke is greatest in the first 24 to 48 hours after TIA with up to half of all subsequent strokes occurring during this time.[31] However, due to the variability in time from symptom onset between the studies, it was not possible to validate the score at 2 days following onset of symptoms in this review.

In spite of its ability to accurately determine stroke risk and triage individuals accordingly, clinical use of the $ABCD^2$ rule has some limitations. There is significant heterogeneity in the $ABCD^2$ calibration analysis (I^2=16%-68% at 7days and 46%-86% at 90 days). Heterogeneity in the studies could be due to a variety of factors. Firstly, study setting and time from onset

of symptoms to clinical assessment varies across studies and the clinical diagnosis of TIA is not performed by a neurologist in all studies. Secondly, methodological quality of the studies needs to be considered. Seven studies do not report if the individual assessing stroke outcome is blinded to the presence of predictors, such as the components of the $ABCD^2$ rule. Therefore the diagnosis of stroke may be modified by knowledge of another reference standard such as imaging. However, all studies report that the WHO definition of stroke was used to define stroke outcome.

Clinical and policy implications

Current international guidelines recommend that individuals with low $ABCD^2$ scores should be triaged for specialist assessment within one week of onset of symptoms. Approximately one third of individuals in our pooled data are in the low risk category and a significant minority of strokes (9.5%) occur in this patient group within 7 days. Therefore it is important that these 'low risk' individuals receive timely treatment to minimise the risk of subsequent stroke. In the hospital setting, imaging evidence of carotid stenosis or DWI abnormality may also serve to assist in the identification of patients at high early risk of stroke after TIA.[32] In terms of implementing the rule in general practice, clinicians need to exert caution when applying the rule as it has only been validated in two population based cohorts. However, the rule does serve to quantify the contribution of the patient's history and physical examination to stratify them according to their risk of developing a subsequent stroke.

National guidelines relating to the management of individuals classified as 'high risk' include early neurology consultation to confirm the diagnosis of TIA, rapid diagnostic assessment,

and implementation of aetiology-specific precautionary measures, including carotid endarterectomy and anticoagulation. However, there is a need for consensus in relation to the identification of individuals at high risk of subsequent stroke. The different cut-points used in the guidelines to categorise stroke risk have considerable economic and management implications. The developers identify three strata of stroke risk after TIA according to $ABCD^2$ rule and we have analysed our data accordingly. However, international consensus on what constitutes a 'low' and 'high' risk patient would serve to improve care, reduce variability, and reduce costs and burden of disease, particularly when evidence is evolving rapidly.

Conclusion

The results of this pooled analysis confirm the ability of the $ABCD^2$ score to correctly predict short term risk of stroke after TIA and also to separate those at lowest, moderate and highest risk of stroke across a wide range of populations and clinical settings. In spite of its limitations, the $ABCD^2$ is easy and quick to administer and it is a useful tool to assist clinicians in the management of individuals with TIA.

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Conflict of interest

No competing interests have been declared.

References

1. Lloyd-Jones D *et al*. Heart disease and stroke statistics – 2010 update: A report from the American Heart Association. *Circulation*. 2010; 121(7):e46-e215.
2. Cumler E, Glasheen J. Risk stratification tools for transient ischemic attack: which patients require hospital admission? *J Hosp Med*. 2009; 4(4):247-251.
3. Coull AJ *et al*. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. 2004: 328(7435):326.
4. Shah KH, Metz HA, Edlow JA. Clinical prediction rules to stratify short-term risk of stroke among patients diagnosed in the emergency department with a transient ischemic attack. *Ann Emerg Med*. 2009; 53(5): 662–73.
5. Rothwell PM *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.
6. Johnson SC, Gress DR, Browner WS, Sidney S. Short term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000; 284(22):2901-2906.
7. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007(9558); 369: 283-292.
8. Giles MF, Rothwell PM. Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischaemic attack risk scores. *Stroke*. 2010; 41(4):667-673.
9. National Institute for Health and Clinical Excellence. *Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA).* http://www.nice.org.uk/nicemedia/pdf/CG68NICEGuideline.pdf, 27 July 2010.

10. Stroke Foundation of New Zealand. *For the assessment and management of people with recent transient ischaemic attack (TIA).* http://www.stroke.org.nz/pdfs/TIA_GuidelineForweb.pdf, 27 July 2010.
11. National Stroke Foundation. *Clinical guidelines for acute stroke management.* http://www.strokefoundation.com.au, 27 July 2010.
12. Easton JD *et al.* Definition and evaluation of transient ischemic attack. A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke* 2009; 40(6): 2276-2293.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009; 339:b2535.
14. Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke. A Classification and Outline of Cerebrovascular Diseases II. *Stroke*. 1975; 6(5): 564-616.
15. Hatano, S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ*. 1976; 54(5): 541-553.
16. McGinn TG *et al.* Users' guide to the medical literature XXII: How to use articles about clinical decision rules. *JAMA*. 2000; 284(1):79-84.
17. Asimos AW *et al.* A multicenter evaluation of the ABCD2 scores accuracy for predicting early ischaemic stroke in admitted patients with transient ischaemic attack. *Ann Emerg Med*. 2010; 55(2): 201-210.

18. Ay H *et al*. Clinical and imaging based prediction of stroke risk after transient ischaemic attack. *Stroke*. 2009; 40(1): 181-186.

19. Calvet D, Touzé 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):187-192.

20. Coutts SB, Eliasziw M, Hill MD, for the VISION study group. An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischaemic attack or minor stroke. *Int J Stroke*. 2008; 3(1): 3-10.

21. Cucchiara BL *et al*. Lipoprotein associated phospholipase A_2 and C-reactive protein for risk stratification of patients with TIA. *Stroke*. 2009; 40(7): 2332-2336.

22. Fothergill A, Christianson TJH, Brown RD, Rabinstein AA. Validation and refinement of the ABCD2 score: a population-based analysis. *Stroke*. 2009; 40(8): 2669-2673.

23. Song T, Lu Z, Bo S, Zhuo L, Rui Z, Yuan G, Yuming X. Clinical application of the $ABCD^2$ score system. *Life Science Journal*. 2009; 6(3): 23-26.

24. Tsivgoulis G, Vassilopoulou S, Spengos K. Potential applicability of the $ABCD^2$ score in triaging patients. *Lancet*. 2007; 369(9567): 1082.

25. Weimar C, Benemann J, Huber R, on behalf of the German Stroke Study Collaboration. Long term mortality and risk of stroke after transient ischaemic attack. *J Neurol*. 2009; 256(4): 639-644.

26. Ong MEH, Chan YH, Lin WP, Chung WL. Validating the $ABCD^2$ score for predicting stroke risk after transient ischemic attack in the ED. *Am J Emerg Med*. 2010; 28(1):44-48

27. Tsivgoulis G *et al*. Multicenter external validation of the $ABCD^2$ score in triaging TIA patients. *Neurology*. 2010; 74(17): 1351-1357.

28. Harrison JK, Sloan B, Dawson J, Lees KR, Morrison DS. The ABCD and the ABCD^2 as predictors of stroke in transient ischemic attack clinic outpatients: a retrospective cohort study over 14 years. *QJM*. 2010; http://qjmed.oxfordjournals.org/cgi/content/full/hcq108v1?view=long&pmid=20601651, 27 July 2010.
29. Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart*. 2006, 92(12):1752-1759.
30. Falk G, Fahey T. Diagnosis in General Practice: Clinical Prediction Rules. *BMJ*. 2009; 339: b2899.
31. Chandratheva A, Mehta Z, Geraghty OC, on behalf of the Oxford Vascular Study. Population based study of risk and predictors of stroke in the first few hours after a TIA. *Neurology*. 2009; 72(22): 1941-1947.
32. Merwick A *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 Neurol. 2010; 9: 1060-69.

Table 1: Guidelines on the management implications of $ABCD^2$ score in the low and high risk groups

National Guidelines	**High Stroke Risk**	**Low Stroke Risk**
NICE - UK Guidelines	**$ABCD^2$ score ≥ 4**	**$ABCD^2$ score < 4**
Assessment	Specialist assessment within 24 hours of onset of symptoms	Specialist assessment as soon as possible, but definitely within 1 week of onset of symptoms
Imaging	Urgent brain imaging (preferably DWMRI) ('urgent' is considered within 24 hours of symptom onset)	Brain imaging within 1 week of onset of symptoms
New Zealand Guidelines	**$ABCD^2$ score ≥ 4**	**$ABCD^2$ score < 4**
Assessment	Specialist assessment within 24 hours of onset of symptoms	Specialist assessment as soon as possible, but definitely within 1 week of onset of symptoms
Imaging	Urgent MRI or CT brain ('urgent' is considered as soon as possible, but certainly within 24 hours)	MRI or CT brain as soon as possible, but certainly within 7 days
Australian Guidelines	**$ABCD^2$ score ≥ 5**	**$ABCD^2$ score < 5**

Assessment	Admitted to a stroke unit (or where available referred to a specialist TIA clinic where the person can be assessed within 24-48 hours) to facilitate rapid assessment and treatment	Managed in the community by a GP, private specialist or where possible referred to a specialist TIA clinic and seen within 7-10 days
Imaging	Urgent CT brain ('urgent' is considered as soon as possible, but certainly within 24 hours).	CT brain and carotid ultrasound (where indicated) as soon as possible (i.e. within 48-72 hours).
US Guidelines	**$ABCD^2$ score ≥ 3**	**$ABCD^2$ score < 3**
Assessment	Admission to hospital for specialist assessment and treatment as soon as possible after the event	Admission to hospital if there is uncertainty that diagnostic workup can be completed within 2 days as an outpatient
Imaging	Undergo neuroimaging evaluation within 24 hours of symptom onset (preferably DWMRI, otherwise CT brain)	Undergo neuroimaging evaluation within 24 hours of symptom onset (preferably DWMRI, otherwise CT brain)

Table 2: Calculation of 7 day stroke risk using derivation study as a predictive model

DERIVATION STUDY[7]			
ABCD^2 risk stratification	**Group (n)**	**Strokes observed (n)**	**Strokes observed (%)**
Low Risk	520	7	1.35
Intermediate risk	921	60	6.51
High risk	469	53	11.3

VALIDATION STUDY[27]				
ABCD^2 risk stratification	**Group (n)**	**Strokes predicted (%)***	**Strokes predicted (n)***	**Strokes observed (n)****
Low Risk	71	1.35	1	2
Intermediate risk	56	6.51	4	5
High risk	21	11.3	2	5

*using original derivation study as a predictive model, ** actual number of strokes reported in each strata of risk

Note: The existing derivation/prognostic model (that is, both the selected variables and their coefficients) is used to predict outcomes for the patients in the validation dataset. The patients' actual outcome (stroke/no stroke) is then compared this prediction. This analysis uses each individual's event probability calculated from their risk score from the original model.

Table 3: Characteristics of studies included in the review

Authors	Study setting	Study type	Participants: n, age, sex	Definition of TIA*	Time from onset of symptoms	Outcomes reported
Johnson et al 2007 (California ED)	Hospital based	Retrospective validation of prospective consecutive cohort	n=1069, 510 males, 559 females	Classic	<24 hours in 99% of admissions	Stroke at 2 days Stroke at 7 days Stroke at 90 days
Johnson et al 2007 (California Clinic)	Hospital based	Retrospective validation of prospective consecutive cohort	n=962, 455 males, 507 females	Classic	< 1 week	Stroke at 2 days Stroke at 7 days Stroke at 90 days
Johnson et al 2007 (Oxford	Population based**	Retrospective validation of prospective	***n=547, 247 males, 300 females	Classic	'assessed as soon as possible after	Stroke at 2 days Stroke at 7 days Stroke at 90 days

Population)		consecutive cohort			the event'	
Johnson et al 2007 (Oxford Clinic)	Hospital based	Retrospective validation of prospective consecutive cohort	n=315, 144 males, 171 females	Classic	'assessed as soon as possible after the event'	Stroke at 2 days Stroke at 7 days Stroke at 90 days
Tsivgoulis et al 2007	Hospital based	Retrospective validation of consecutive admissions using medical charts	n=226, 133 males, 93 females mean age 63.9 years	Classic	<48 hours	Stroke at 7 days Stroke at 30 days
Coutts et al 2008	Hospital based	Prospective consecutive cohort	n=87	Classic	< 12 hours	Stroke at 30 Stroke at 90 days
Asimos et al 2009	Hospital based	Retrospective validation of non-consecutive	†n=1667, 754 males, 913 females mean age 67.4	Classic	< 24 hours	Stroke at 7 days

		admissions using medical charts	years			
Ay et al 2009	Hospital based	Retrospective validation of consecutive admissions using medical charts	n=477, 231 males, 246 females, mean age 67.7 years	Classic	< 24 hours	Stroke at 7 days
Calvet et al 2009	Hospital based	Retrospective validation of prospective consecutive cohort	n=343, 212 males, 131 females mean age 62.4 years	Classic	< 48 hours	Stroke at 7 days Stroke at 3 months
Cucchiara et al 2009	Hospital based	Prospective consecutive cohort	n=167, 75 males, 92 females mean age 62 years	Classic	< 48 hours	Stroke at 90 days

Fothergill et al 2009	Population based**	Retrospective validation of consecutive admissions using medical charts	n=284, 126 males, 158 females mean age 71.9 years	Classic	< 72 hours	Stroke at 7 days Stroke at 30 days Stroke at 365 days
Song et al 2009	Hospital based	Prospective consecutive cohort	n=136	Classic	< 48 hours	Stroke at 2 days Stroke at 7 days
Weimar et al 2009	Hospital based	Retrospective validation of prospective consecutive cohort	††n=1448, 778 males, 670 females mean age 67.6 years	Classic	<24 hours in 91.9% of admissions	Stroke at 90 days
Ong et al 2010	Hospital based	Retrospective validation of consecutive admissions using	n=470, 293 males, 177 females mean age 61 years	Classic	Unreported	Stroke at 2 days Stroke at 7 days Stroke at 30 days Stroke at 90 days

		computerised medical charts				
Tsivgoulis et al 2010	Hospital based	Prospective consecutive cohort	n=148, 82 males, 66 females mean age 60 years	Classic	Unreported	Stroke at 7 days Stroke at 90 days
Harrison et al 2010	Hospital based	Retrospective validation of prospective consecutive cohort	‡n=795, 342 males, 453 females mean age 67 years	Classic	Unreported	Stroke at 90 days Stroke at 1 year Stroke at 5 years Stroke at 10 years

* Classic definition of TIA – 'A sudden focal neurologic deficit lasting less than 24 hours, of presumed vascular origin, and confined to an area of the brain or eye perfused by a specific artery'[14]

**Population based – participants were recruited from general practice, outpatient clinics and hospital settings

***data analysed in 543 individuals only

†data was analysed in 1054 individuals only

††data was analysed in 1411 individuals only

‡data was analysed in 789 individuals only

Table 4: Methodological quality of studies included in the review (McGinn Criteria)

	Were those assessing the outcome event blinded to presence of predictors?	Were those assessing the presence of predictors blinded to the outcome event?	Was there ≥80% follow up of those enrolled?	Were patients selected in an unbiased fashion?	Do patients represent a wide spectrum of severity of disease?
Johnson et al 2007 (California ED)	Unreported	Yes	Unreported	Yes	Yes
Johnson et al 2007 (California clinic)	Unreported	Yes	Unreported	Yes	No
Johnson et al 2007 (Oxford population)	Unreported	Yes	Yes	Yes	Yes
Johnson et al 2007 (Oxford clinic)	Unreported	Yes	Unreported	Unreported	Yes
Tsivgoulis et al 2007	Unreported	Yes	Yes	Yes	Yes
Coutts et al 2008	Unreported	Yes	Unreported	Yes	Yes
Asimos et al 2009	Yes	No	No	No	No
Ay et al 2009	Yes	Unreported	No	Yes	Yes
Calvet et al 2009	Yes	Yes	Yes	Yes	Yes
Cucchiara et al 2009	Yes	Yes	Yes	Unreported	Yes
Fothergill et al 2009	Unreported	Yes	Yes	Yes	Yes
Song et al 2009	Unreported	Yes	Yes	Yes	Unreported
Weimar et al 2009	Unreported	Unreported	Yes	Yes	Yes
Ong et al 2010	Unreported	Unreported	Yes	Yes	Yes
Tsivgoulis et al 2010	Yes	Yes	Yes	Yes	Yes
Harrison et al 2010	Unreported	Unreported	Yes	Yes	No

Table 5: Sensitivity and specificity conventional $ABCD^2$ score cut-off

$ABCD^2$ dichotomisation (as per international guidelines)	**Diagnostic accuracy (95% confidence interval)**			
$ABCD^2$ ≥3	**Sensitivity**	**Specificity**	**Likelihood ratio (+)**	**Positive predictive value**
7 days	0.96 (0.94-0.98)	0.17 (0.16-0.18)	1.16 (1.13-1.19)	7.4% (6.7-8.2%)
90 days	0.94 (0.92-0.96)	0.17 (0.16-0.18)	1.14 (1.11-1.17)	7.8% (7.1-8.6%)
$ABCD^2$ ≥4				
7 days	0.90 (0.87-0.93)	0.36 (0.34-0.37)	1.40 (1.35-1.46)	8.8% (7.9-9.7%)
90 days	0.86 (0.82-0.89)	0.36 (0.33-0.38)	1.35 (1.29-1.41)	9.1% (8.2-10%)
$ABCD^2$ ≥5				
7 days	0.70 (0.65-0.74)	0.60 (0.59-0.62)	1.77 (1.64-1.90)	10.9% (9.7-12.2%)
90 days	0.63 (0.58-0.68)	0.61 (0.59-0.62)	1.59 (1.47-1.73)	10.5% (9.3-11.8%)

Figure 1: Summary of the ABCD^2 score

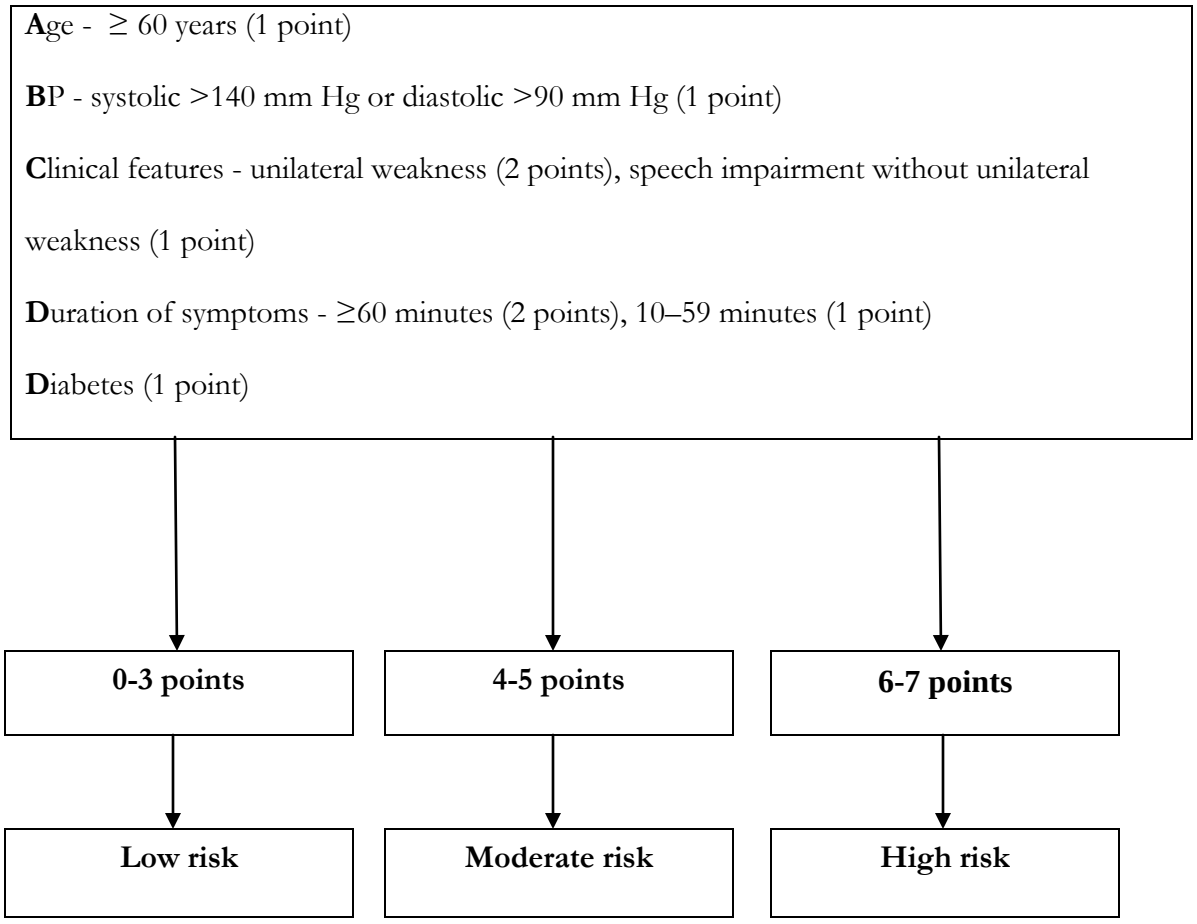
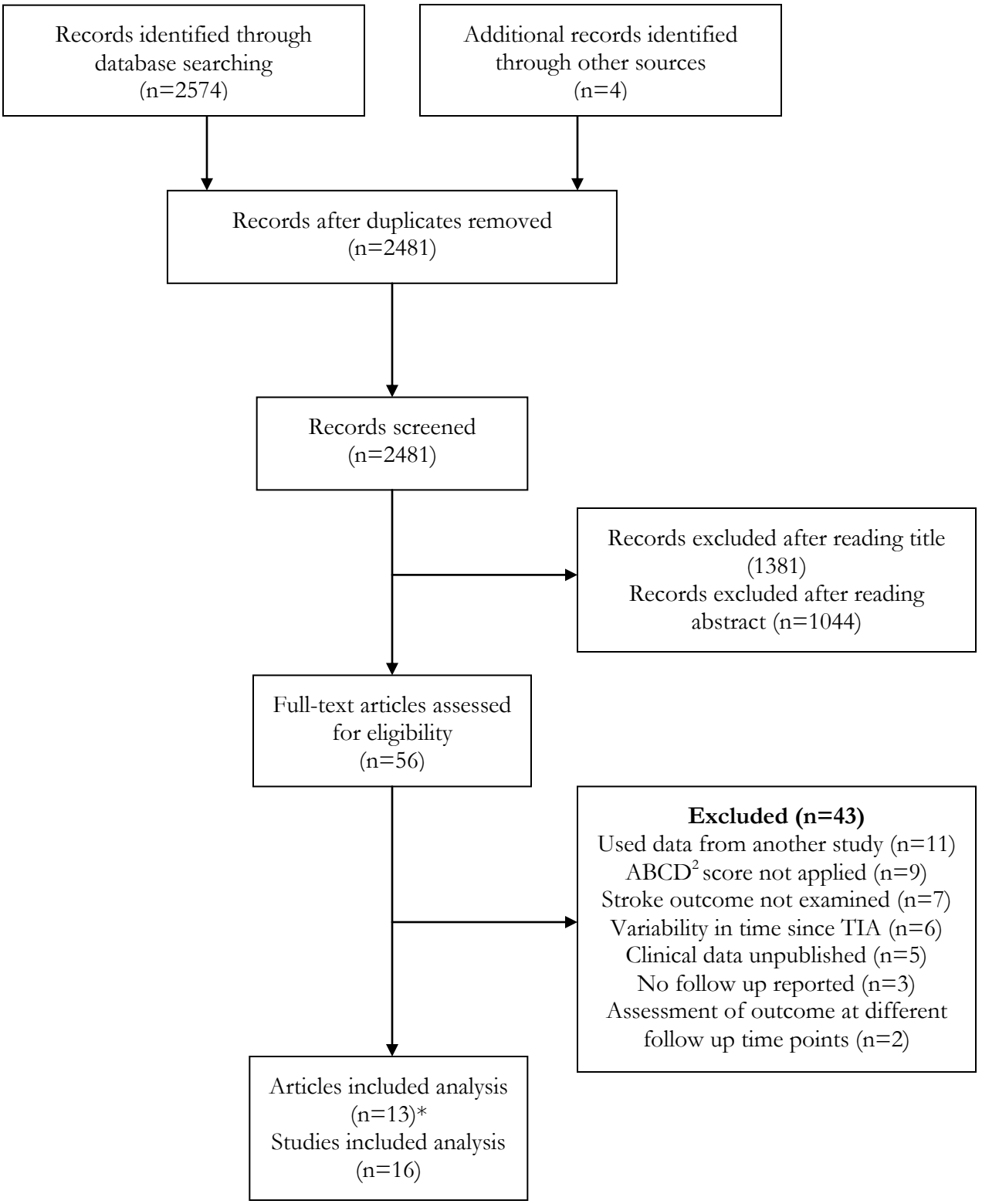


Figure 2: Search strategy



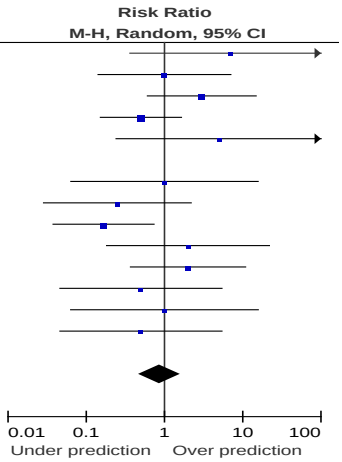
*One article contained data on 4 different cohorts

Figure 3: Prediction of 7 day risk of stroke across the three risk strata

Low risk (0-3 points)

Study or Subgroup	Predicted Events	Predicted Total	Observed Events	Observed Total	Weight	Risk Ratio M-H, Random, 95% CI
Asimos et al 2010	3	231	0	231	3.9%	7.00 [0.36, 134.76]
Ay et al 2009	2	162	2	162	8.1%	1.00 [0.14, 7.01]
California clinic 2007	6	426	2	426	11.2%	3.00 [0.61, 14.78]
California ED 2007	4	259	8	259	17.2%	0.50 [0.15, 1.64]
Calvet et al 2009	2	139	0	139	3.7%	5.00 [0.24, 103.21]
Coutts et al 2008	0	9	0	9		Not estimable
Cucchiara et al 2009	1	61	1	61	4.4%	1.00 [0.06, 15.63]
Fothergill et al 2009	1	71	4	71	6.8%	0.25 [0.03, 2.18]
Ong et al 2010	2	145	12	145	12.6%	0.17 [0.04, 0.73]
Oxford clinic 2007	2	162	1	162	5.7%	2.00 [0.18, 21.84]
Oxford population 2007	4	261	2	261	10.3%	2.00 [0.37, 10.82]
Song et al 2009	1	72	2	72	5.8%	0.50 [0.05, 5.39]
Tsivgoulis et al 2007	1	84	1	84	4.4%	1.00 [0.06, 15.73]
Tsivgoulis et al 2010	1	71	2	71	5.8%	0.50 [0.05, 5.39]
Total (95% CI)		**2153**		**2153**	**100.0%**	**0.86 [0.47, 1.58]**
Total events	30		37			

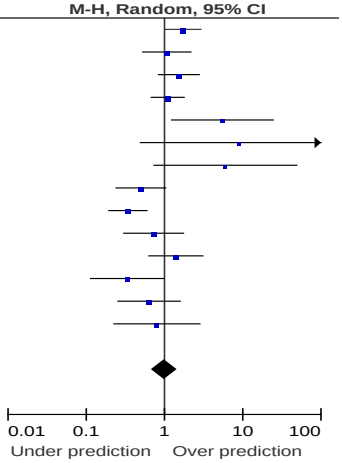
Heterogeneity: Tau² = 0.19; Chi² = 14.23, df = 12 (P = 0.29); I² = 16%
Test for overall effect: Z = 0.48 (P = 0.63)



Moderate risk (4-5 points)

Study or Subgroup	Predicted Events	Predicted Total	Observed Events	Observed Total	Weight	Risk Ratio M-H, Random, 95% CI
Asimos et al 2010	36	559	21	559	10.0%	1.71 [1.01, 2.90]
Ay et al 2009	15	227	14	227	8.7%	1.07 [0.53, 2.17]
California clinic 2007	26	397	17	397	9.5%	1.53 [0.84, 2.77]
California ED 2007	33	506	30	506	10.3%	1.10 [0.68, 1.78]
Calvet et al 2009	11	173	2	173	4.4%	5.50 [1.24, 24.45]
Coutts et al 2008	4	58	0	58	1.6%	9.00 [0.50, 163.46]
Cucchiara et al 2009	6	85	1	85	2.7%	6.00 [0.74, 48.78]
Fothergill et al 2009	10	150	20	150	8.6%	0.50 [0.24, 1.03]
Ong et al 2010	15	226	44	226	9.7%	0.34 [0.20, 0.59]
Oxford clinic 2007	8	119	11	119	7.5%	0.73 [0.30, 1.74]
Oxford population 2007	14	216	10	216	8.1%	1.40 [0.64, 3.08]
Song et al 2009	4	58	12	58	6.3%	0.33 [0.11, 0.97]
Tsivgoulis et al 2007	7	113	11	113	7.3%	0.64 [0.26, 1.58]
Tsivgoulis et al 2010	4	56	5	56	5.4%	0.80 [0.23, 2.82]
Total (95% CI)		**2943**		**2943**	**100.0%**	**0.99 [0.67, 1.47]**
Total events	193		198			

Heterogeneity: Tau² = 0.33; Chi² = 40.26, df = 13 (P = 0.0001); I² = 68%
Test for overall effect: Z = 0.04 (P = 0.97)



High risk (6-7 points)

Study or Subgroup	Predicted Events	Predicted Total	Observed Events	Observed Total	Weight	Risk Ratio M-H, Random, 95% CI
Asimos et al 2010	30	264	19	264	12.5%	1.58 [0.91, 2.73]
Ay et al 2009	10	88	7	88	8.0%	1.43 [0.57, 3.58]
California clinic 2007	16	139	10	139	9.8%	1.60 [0.75, 3.40]
California ED 2007	34	304	33	304	13.9%	1.03 [0.66, 1.62]
Calvet et al 2009	4	31	3	31	4.5%	1.33 [0.32, 5.47]
Coutts et al 2008	2	20	0	20	1.3%	5.00 [0.26, 98.00]
Cucchiara et al 2009	2	21	2	21	2.9%	1.00 [0.16, 6.45]
Fothergill et al 2009	7	64	12	64	8.5%	0.58 [0.25, 1.39]
Ong et al 2010	11	99	32	99	11.4%	0.34 [0.18, 0.64]
Oxford clinic 2007	4	34	5	34	5.6%	0.80 [0.23, 2.73]
Oxford population 2007	7	66	17	66	9.1%	0.41 [0.18, 0.93]
Song et al 2009	1	6	2	6	2.3%	0.50 [0.06, 4.15]
Tsivgoulis et al 2007	3	29	6	29	5.2%	0.50 [0.14, 1.81]
Tsivgoulis et al 2010	3	21	5	21	5.1%	0.60 [0.16, 2.20]
Total (95% CI)		**1186**		**1186**	**100.0%**	**0.84 [0.60, 1.19]**
Total events	134		153			

Heterogeneity: Tau² = 0.17; Chi² = 24.24, df = 13 (P = 0.03); I² = 46%
Test for overall effect: Z = 0.96 (P = 0.34)

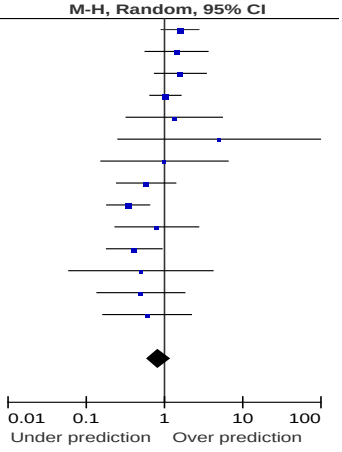
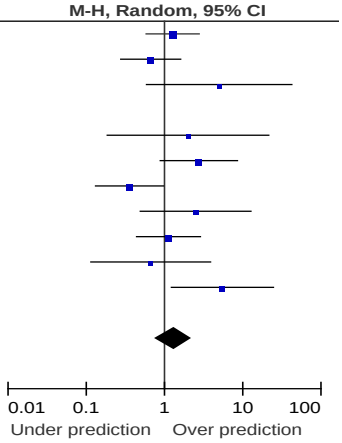


Figure 4: Prediction of 90 day risk of stroke across the three risk strata

Low risk (0-3 points)

Study or Subgroup	Predicted Events	Predicted Total	Observed Events	Observed Total	Weight	Risk Ratio M-H, Random, 95% CI
California clinic 2007	14	426	11	426	15.8%	1.27 [0.58, 2.77]
California ED 2007	8	259	12	259	14.5%	0.67 [0.28, 1.60]
Calvet et al 2009	5	139	1	139	5.0%	5.00 [0.59, 42.25]
Coutts et al 2008	0	9	0	9		Not estimable
Cucchiara et al 2009	2	61	1	61	4.2%	2.00 [0.19, 21.48]
Harrison et al 2010	11	329	4	329	11.5%	2.75 [0.88, 8.55]
Ong et al 2010	5	145	14	145	13.0%	0.36 [0.13, 0.97]
Oxford clinic 2007	5	162	2	162	7.4%	2.50 [0.49, 12.70]
Oxford population 2007	9	261	8	261	13.7%	1.13 [0.44, 2.87]
Tsivgoulis et al 2010	2	71	3	71	6.7%	0.67 [0.11, 3.87]
Weimar et al 2009	11	343	2	343	8.3%	5.50 [1.23, 24.63]
Total (95% CI)		**2205**		**2205**	**100.0%**	**1.31 [0.77, 2.23]**
Total events	72		58			

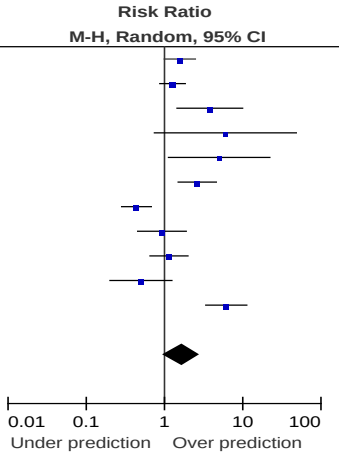
Heterogeneity: Tau² = 0.31; Chi² = 16.66, df = 9 (P = 0.05); I² = 46%
Test for overall effect: Z = 0.98 (P = 0.32)



Moderate risk (4-5 points)

Study or Subgroup	Predicted Events	Predicted Total	Observed Events	Observed Total	Weight	Risk Ratio M-H, Random, 95% CI
California clinic 2007	44	397	28	397	10.7%	1.57 [1.00, 2.47]
California ED 2007	57	506	45	506	11.0%	1.27 [0.87, 1.84]
Calvet et al 2009	19	173	5	173	8.4%	3.80 [1.45, 9.95]
Coutts et al 2008	6	58	1	58	4.1%	6.00 [0.75, 48.29]
Cucchiara et al 2009	10	85	2	85	6.0%	5.00 [1.13, 22.14]
Harrison et al 2010	42	373	16	373	10.3%	2.63 [1.50, 4.58]
Ong et al 2010	25	226	57	226	10.8%	0.44 [0.28, 0.68]
Oxford clinic 2007	13	119	14	119	9.6%	0.93 [0.46, 1.89]
Oxford population 2007	24	216	21	216	10.3%	1.14 [0.66, 1.99]
Tsivgoulis et al 2010	6	56	12	56	8.6%	0.50 [0.20, 1.24]
Weimar et al 2009	74	660	12	660	10.1%	6.17 [3.38, 11.24]
Total (95% CI)		**2869**		**2869**	**100.0%**	**1.64 [0.98, 2.77]**
Total events	320		213			

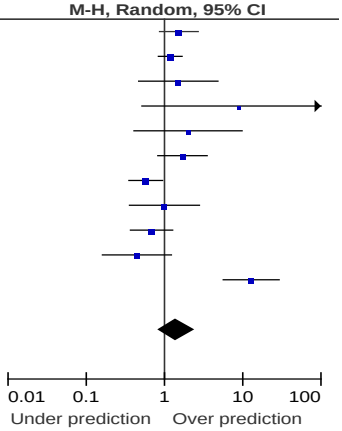
Heterogeneity: Tau² = 0.60; Chi² = 73.20, df = 10 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.87 (P = 0.06)



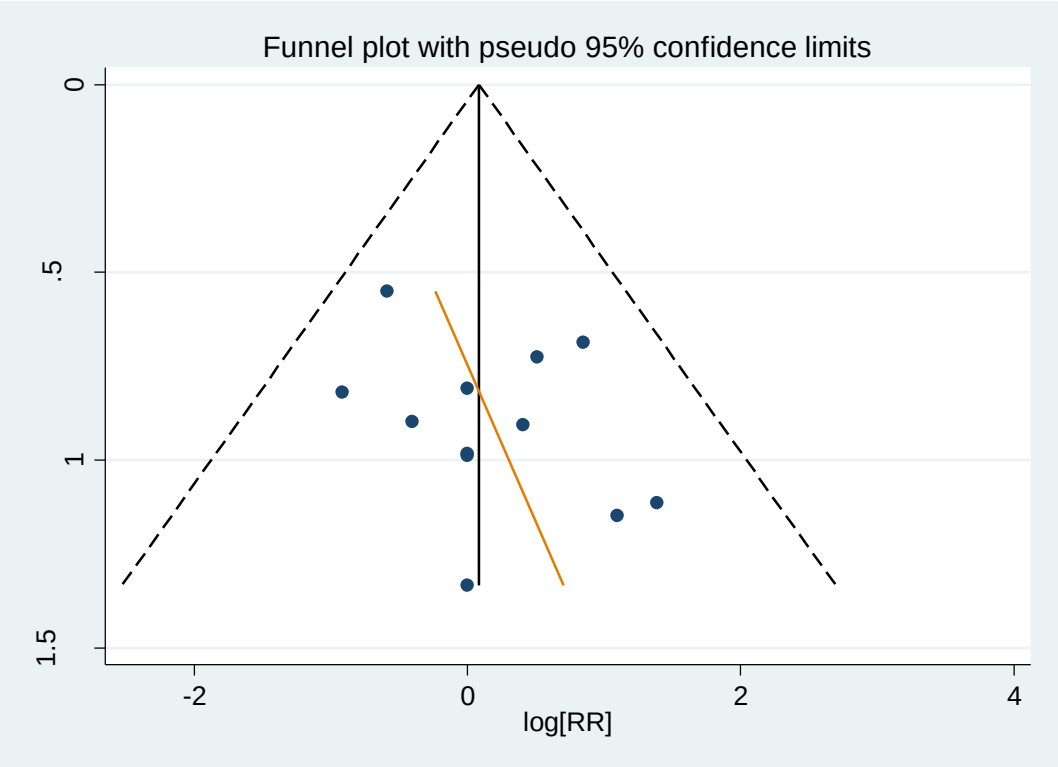
High risk (6-7 points)

Study or Subgroup	Predicted Events	Predicted Total	Observed Events	Observed Total	Weight	Risk Ratio M-H, Random, 95% CI
California clinic 2007	26	139	17	139	11.1%	1.53 [0.87, 2.69]
California ED 2007	58	304	49	304	12.0%	1.18 [0.84, 1.67]
Calvet et al 2009	6	31	4	31	8.0%	1.50 [0.47, 4.80]
Coutts et al 2008	4	20	0	20	2.8%	9.00 [0.52, 156.91]
Cucchiara et al 2009	4	21	2	21	6.1%	2.00 [0.41, 9.77]
Harrison et al 2010	17	87	10	87	10.3%	1.70 [0.83, 3.50]
Ong et al 2010	19	99	33	99	11.5%	0.58 [0.35, 0.94]
Oxford clinic 2007	6	34	6	34	8.7%	1.00 [0.36, 2.79]
Oxford population 2007	13	66	19	66	10.9%	0.68 [0.37, 1.27]
Tsivgoulis et al 2010	4	21	9	21	8.8%	0.44 [0.16, 1.22]
Weimar et al 2009	77	408	6	408	9.8%	12.83 [5.66, 29.12]
Total (95% CI)		**1230**		**1230**	**100.0%**	**1.40 [0.81, 2.40]**
Total events	234		155			

Heterogeneity: Tau² = 0.60; Chi² = 57.16, df = 10 (P < 0.00001); I² = 83%
Test for overall effect: Z = 1.21 (P = 0.23)



Appendix 1: Funnel plot of studies included in the 7 day analysis



Appendix 2: Funnel plot of studies included in the 90 day analysis