National Institute for Health and Care Excellence

Draft for consultation

# Atrial fibrillation

## Tools to predict stroke

*NICE guideline*

*Evidence reviews*

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*Draft for Consultation*

*Developed by the National Guideline Centre, hosted by the RCP*

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# Contents

# 1 Introduction

The risk of stroke caused by thromboembolism is up to 20% higher in patients with atrial fibrillation. The risk increases in the presence of additional risk factors, such as, hypertension, diabetes and high cholesterol.

Risk stratification tools help to predict the risk of embolic stroke in patients with atrial fibrillation and the presence of these other cardiovascular risks. The tools help to identify the risk of multiple risk factors, and based on this information, the clinician and patient can decide if the patient will benefit from anti-coagulation (e.g. DOAC or Vitamin K antagonists).

However Vitamin K antagonists and DOACs are not without risk. They increase the risk of bleeding, particularly in the elderly; hence the use of tools to predict the bleeding risk in patients exposed to these medications is also important. Knowing the predicted benefit of reducing the risk of stroke as well as the increased risk of bleeding helps the clinician and patient to make an informed decision about whether to use these anti-coagulants. The tools also help to discuss the recommendation with patients.

This chapter will outline the best tools available to assess the risk-benefit ratio of anti-coagulation in patients with atrial fibrillation. The high cost of the newer oral anti-coagulants in comparison to Vitamin K antagonists need to also be taken into account and a cost benefit analysis is presented. This is presented in two parts: a review of the clinical effectiveness of the tools, followed by a review of the accuracy of the tools.

# 2 Effectiveness of tools to predict stroke or thromboembolic events in people with atrial fibrillation

## 2.1 Review question: What is the most clinically and cost-effective risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation?

## 2.2 PICO table

For full details see the review protocol in appendix A.

**Table 1: PICO characteristics of review question**

| | |
|---|---|
| **Population** | People aged over 18 with a diagnosis of AF. |
| **Intervention(s)** | Any stroke risk tool (for example, ABC stroke score, Q stroke, ATRIA, Troponin 2, CHADS2).<br>Any version of CHADS2VASC with modifications<br><br>[Note: **treat each test using a different threshold as a separate intervention**]. |
| **Comparison(s)** | CHADS2VASC (the established method, as recommended by previous version of this guideline) |
| **Outcomes** | Critical<br>• health-related quality of life<br>• mortality<br>• stroke or thromboembolic complications<br>• major bleeding |
| **Study design** | Randomised controlled trials |

## 2.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[83] Methods specific to this review question are described in the review protocol in appendix A.

This review is not a 'prognostic accuracy' review, but is instead a review of trials that have compared later health outcomes in people randomised to different prediction tools. Tools with differing prognostic accuracies may differ in their influence on later health outcomes through stimulating a more or less appropriate treatment approach. Whilst accuracy is not measured directly in such randomised trials, the advantage of such studies is that they demonstrate clinical efficacy. In contrast a prognostic accuracy study can only demonstrate the intrinsic predictive accuracy of the tool and is unable to show that the accuracy affects health outcomes. However such randomised trials are not commonly undertaken, and may provide equivocal results, and so a prognostic accuracy review has also been undertaken (section 3).

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

## 2.4 Clinical evidence

### 2.4.1 Included studies

No relevant clinical studies comparing different stroke risk tools with CHADS2VASC were identified.

### 2.4.2 Excluded studies

See the excluded studies list in appendix I.

### 2.4.3 Summary of clinical studies included in the evidence review

No evidence identified.

### 2.4.4 Quality assessment of clinical studies included in the evidence review

No evidence identified.

## 2.5 Economic evidence

### 2.5.1 Included studies

No relevant health economic studies were identified.

### 2.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

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

## 2.6 The committee's discussion of the evidence

No evidence was generated by this review. The committee discussed the predictive accuracy evidence (see section 3 below only, as this was felt to be sufficient to inform recommendations relevant to the most appropriate methods to predict stroke in people with AF, without the need for any consensus recommendations or research recommendations pertaining to this review.

# 3 Accuracy of tools to predict stroke or thromboembolic events

## 3.1 Review question: What is the most accurate risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation?

For full details see review protocol in Appendix A.

**Table 2: 'PICO' characteristics of review question**

| Question | |
|---|---|
| Population | People aged >18 with a diagnosis of atrial fibrillation, who are not on anticoagulants |
| Risk tool | Any stroke risk tool (e.g., ABC stroke score, Q stroke, ATRIA, Troponin 2, CHADSVASC, CHADS2)<br>Any other version of CHADSVASC with modifications |
| Reference standard | Later stroke and/or thromboembolic event at follow up used in study |
| Outcomes (in terms of predictive test accuracy, calibration) | Simple diagnostic (prognostic) accuracy outcomes, such as sensitivity and specificity<br>C statistic (based on sensitivity and specificity but useful if >1 threshold used).<br>Calibration outcomes<br>Reclassification |
| Study types | cohort (external validation, internal validation) |
| Specific groups | Ethnic groups |

## 3.2 Clinical evidence

The aim of this review was to evaluate the accuracy of stroke/thromboembolism (TE) prediction tools with reference to their discriminatory capabilities (sensitivity, specificity, C statistics, D statistics), calibration (R2 and Hosmer-Lemeshow statistics) and the Net Reclassification Index (NRI) in people with AF. The reference standard was the incidence (or not) of stroke and/or systemic thromboembolism (TE) at follow up.

We therefore searched for cohort studies evaluating stroke/TE prediction tools for people with AF. Only studies which analysed predictive accuracy in people who were not anticoagulated at baseline were included. If a study containing anticoagulated patients also contained a separately analysed sub-group who were not on anticoagulants then the study was also included, although only the data from the non-anticoagulated sub-group were included in the review. Non-anticoagulated cohorts were used because the purpose of stroke prediction tools is to evaluate who *requires* anticoagulation – that is, those people who are at risk of stroke if anticoagulants are *not* taken. For such a risk to be accurately estimated requires that the tool has been validated (with reference to later incidence of stroke/TE) in an analogous non-anticoagulated population. In contrast, use of an anticoagulated cohort would involve the stroke prediction tools identifying those people that have stroke/TE *despite* anticoagulation, which are not necessarily the people that require anticoagulation.

Nevertheless, non-anticoagulated cohorts present problems of their own. If a modern cohort is not anticoagulated this may mean that it is deemed very low risk or that it is 'special' in some way (perhaps by having contraindications to Warfarin or DOACS). This would make

such a cohort unrepresentative of the vast population of people with AF who have been recently diagnosed, and so the predictive capabilities of risk tools in such a cohort might differ from those in the target population. Hence during this review attention has been focussed upon the reasons why the cohort was not anti-coagulated, and whether the characteristics of the cohorts were noticeably different from the general population of people with AF. In general, the non-anticoagulated cohorts included in this review appear not to be low risk, nor do they seem 'special' in any way.

37 studies evaluating the accuracy of stroke/thromboembolism prediction tools for people with atrial fibrillation who were not anticoagulated were included in the review.[2, 3, 10, 20, 27, 30, 33, 35, 36, 38, 46, 57, 63, 65, 68, 71-73, 77, 79, 80, 88-90, 93, 113-115, 118, 121, 122, 124, 127-131, 133] These studies are summarised in Table 3. The different stroke prediction tools are outlined in Table 4.

Quality of data was generally low or very low. This was partly due to serious or very serious risk of bias in all studies resulting from poor reporting of blinding of prediction tool and outcome data (and vice versa), and from a majority of studies having excessively short follow up periods (<5 years) and/or a relatively low number of events at follow up (<100). In addition, some pooled effects showed serious heterogeneity. This heterogeneity remained unexplained as we had not proposed any pre-hoc sub-grouping strategies.

Evidence from these studies is summarised in the GRADE clinical evidence profiles below (Table 5 to Table 10). See also the study selection flow chart in Appendix B:, study evidence tables in Appendix F:, forest plots in Appendix D:, and excluded studies list in Appendix I:. In summary, there did not appear to be clinically important differences in accuracy between different tools.

## 1 Summary of included studies

### 2 Table 3: Summary of studies included in the review

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| Abraham 2013[2] | CHADS2<br>CHADSVASC | 5981 post-menopausal women with NVAF from USA. 64.9 hypertensive, 3.7% CHF, 9.2% DM, 2.6% prior stroke, 4.9% prior TIA, 10% prior CAD. | Stroke/TIA obtained from medical records and centrally adjudicated | 457 | Median 11.8 years |
| Abumaileq 2015a[3] | CHADSVASC<br>R2CHADS2<br>ATRIA | 154 consecutive patients with NVAF from Spain. Mean age was 74 years, mean SBP was 129, 30% were current smokers, 21% had DM, 6.5% had HF, 15% CHD. 85% CHADSVASC score of 2 points or more | TE event (Stroke/TIA, PE, Peripheral embolism) during follow-up. Stroke needed to last >24 hours and shown on CT/MRI with confirmation from a neurologist. A diagnosis of peripheral embolism was defined as non-central nervous system embolism with clinical or radiographic evidence of arterial occlusion. | 9 | 11 months |
| Aspberg 2016[10] | ATRIA<br>CHADS2<br>CHADSVASC | 115,153 participants with AF from Sweden. 80.6% percent had score of 2 or more on CHADSVASC. Prior stroke 13%, 70.7% >65 years, 49.3% female, 15.8% DM, 28% HF, 6% Renal failure, 44% hypertension. | Acute ischaemic stroke (defined by ICD-10 code I63), excluding TIAs or other kinds of thromboembolism. The outcome diagnosis, ischaemic stroke, was retrieved from the National Patient Register. | 11052 | Up to 5 years |
| Chao 2016[20] | CHADSVASC<br>Age-modified CHADSVASC | 124, 271 patients with AF (diagnosed using ICD-9-CM code from the National health Insurance Research database in Taiwan). Age | Ischaemic stroke, with concomitant imaging studies of the brain (CT/MRI) | 21,008 | Up to 10 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | 72, 54% male, 56.8% hypertensive, 23% DM, 38% CHF, 28% previous stroke/TIA. Median CHADSVASC score 3. | | | |
| Fang 2008[27] | AFI 1994<br>SPAF<br>CHADS2<br>Framingham<br>ACCP 2004 | 5,588 patients with NVAF from USA. Sample data not given for this cohort. 81.3% at moderate or high risk of stroke | Hospital database searched for incident thromboembolic events, either ischemic stroke or other peripheral embolism. The validity of potential events was adjudicated by an outcomes committee of 3 physicians using a formal study protocol. If there was no consensus on the validity of an event, an expert neurologist adjudicated the event. Outcome events that occurred during hospitalization or as a complication from a diagnostic or interventional procedure were excluded | 685 | 6 years |
| Fox, 2017[30] | GARFIELD<br>CHADSVASC | 2301 people with AF. Demographic data not available | Composite of IS, SE and TIA | 51 | 3 years |
| Friberg 2012b[33] | CHADSVASC, CHADS2, revised CHADS2, SPAF 1999, AFI 1994, ACC/AHA/ESC, Framingham, NICE | 90, 490 patients with AF defined by ICD-10 code 1489 with or without subscales A-F from Sweden. Demographic data not available. | First occurrence of Ischaemic stroke (defined by ICD-10 code 163). Events in first 14 days post inception excluded. | 5359 | 1.4 years |
| Gage 2004 [35] | AFI 1994, SPAF 1995, ACCP 2001, CHADS2, Framingham | 2580 patients with NVAF from 6 international RCTs. 37% women, mean age 72, 46% hypertension, 25% HF, 13% DM, 22% prior stroke or TIA, 18% prior MI/angina. 59% moderate or high risk. | Suspected stroke, confirmed by CT in 98% of incident neurological events. Strokes defined as neurological deficits that persisted > 24 hours and not associated with an intracranial haemorrhage. | 207 | 1.9 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| Gage 2001[36] | CHADS2<br>AFI 1994<br>SPAF 1995 | 1733 patients from the US National Registry of AF cohort. Mean age 81, 58% women, 56% CHF, 56% hypertension, 23% DM, 25% history of cerebral ischaemia. 1204 were not prescribed any antithrombotic therapy and 529 (31%) were prescribed aspirin. CHADS2 score of 2.1. | Hospitalisation for ischaemic stroke as determined by Medicare claims. ICD-9-CM codes used to identify.<br>1.2 year FU | 94 | 1.2 years |
| Guo 2013[38] | CHADS2<br>CHADSVASC | 885 patients with pre-existing diagnosis of permanent, persistent or paroxysmal AF at General Hospital in China between 2007 and 2010. Mean age 77, 27% female, 75% hypertensive, 39% DM, 23% HF, 63% CAD, 20.9% prior stroke, renal failure 9.6%. 81.2% high risk on CHADSVASC. | Major adverse events (stroke/TE). IS defined as focal neurological deficit of sudden onset lasting >24 hours diagnosed clinically by a neurologist. A TE was IS, PE or peripheral embolism. | 85 | 1.9 years |
| Hippisley Cox 2013[46] | Q stroke<br>CHADS2<br>CHADSVASC | 7689 people with NVAF from UK. 71% percent high risk on CHADS2. People with prior stroke or TIA excluded. Demographic data not available for this cohort. | Stroke/TIA, excluding haemorrhagic stroke, as defined by ICD-10 codes: cerebral infarction (I63) and stroke not specified as haemorrhage or infarction (I64). | 890 | Up to 10 years |
| Kang 2017[57] | CHADS2<br>CHADSVASC | 10,846 patients with newly diagnosed NVAF from South Korea. Mean age | Ischaemic stroke. Stroke was defined according to ICD-10 codes (I63-64) for diagnoses made during hospitalization and | 888 | 1.2 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | 63.7 years, 47% women, previous stroke 16.7%, CHF 25%, DM 21%, IHD 48%, CHADS more than or equal to 4: 16%, CHADSVASC more than or equal to 6: 10%. | according to brain imaging such as computed tomography and magnetic resonance imaging | | |
| Kim 2017[63] | CHADS2, CHADSVASC, ATRIA | 5855 NVAF patients from South Korea. Mean age 64, 48% women, CHADSVASC means core 3.28, 24.5% prior stroke, 13% MI, 32% HF, 76% hypertension, 20% DM. | The primary end point was incident ischemic stroke (including ischemic stroke–related death). Diagnosis made with concomitant brain imaging studies, including computed tomography or MRI. | 819 | 4.2years |
| Larsen 2012[68] | CHADS2<br>CHADSVASC | 1603 patients with incident AF (defined by ICD-08 [pre 1994] or ICD-10 codes) from a Danish cohort of 57,053 middle aged people. Age 67, 40% women, mean follow up 5.4 years, CHF 24.4%, 30% hypertension, 10% DM, 6% stroke history. 7% CHADS2 of 5 or above, 6% CHADSVASC score of 5 or above. | Stroke (not defined) | unclear | 5.4 years |
| Lip 2006[71] | CHADS2, CHADSVASC (Birmingham 2009), CHADS2 with vWF, Birmingham with vWF | 994 patients with NVAF, from USA. Mean age 69.3, 75% male, 53% hypertension, 14% diabetes, 19% recent HF, 13% previous TIA/stroke, 10% previous MI, 6% PVD, 9% LV systolic dysfunction, | Ischaemic stroke (not defined) | unclear | 1.6 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | 8% current smokers. 43 IS events. 73.9% not low risk according to CHADS2. | | | |
| Lip 2010[72] | AFI 1994, SPAF 1999, CHADS2, revised CHADS2, Framingham, NICE, ACCA/AHA/ESC, ACCP 2008 and CHADSVASC (Birmingham) | 1084 NVAF patients from USA. Age 66 years, 41% women, previous stroke 4.2%, TIA 4.3%, DM 17.3%, hypertension 67%, HF 23.5%, antiplatelets 74%, LVEF 53%. 17% classed as high risk and 61.9% as intermediate risk on CHADS2 | Thromboembolic events: IS (focal neurological event lasting >24 hours diagnosed by neurologist), PE or peripheral embolism | 25 | 1 year |
| Lip 2014[73] | SAMe-TT2R2 | 3,483 patients with AF (n=242 had valvular AF) who were not receiving OACs. Mean age 70, 43% female, 48% HF, 33% CAD, 17% previous MI, 5% previous CABG, 40% hypertensive, 7% previous stroke, 9% renal insufficiency. Mean CHADSVASC score 3.1. | Stroke/ TEs (not defined) | 273 | Up to 10 years |
| Maheshwari, 2019[77] | CHADSVASC<br>P2-CHADSVASC | 2229 participants from the ARIC study (Atherosclerosis Risk in Communities) and 700 participants from MESA (Multi-Ethnic Study of Atherosclerosis) with incident AF who were not on anticoagulants within 1 year of AF diagnosis; | Ischaemic stroke | 47 (ARIC)<br>31 (MESA) | 1 year (5 years for ARIC CHADSVASC) |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | ARIC cohort: age 73; female 47%; DM 30%; hypertension 75%; previous MI 24%; HF 38%; PAD 9%; past stroke/TIA 15%; CHADSVASC 3.6; black 19%, white 81%;<br>MESA cohort: age 76; female 45%; DM 18%; hypertension 68%; previous MI 6%; HF 8%; PAD 2%; past stroke/TIA 6%; CHADSVASC 3.0; black 20%, white 49%; Chines 13%; Hispanic 17% | | | |
| McAlister, 2017[79] | CHADS2, CHADSVASC, R2CHADS2 (71 point), ATRIA, CHADS2KDIGO, CHADS2Alb, CHADS2 eGFR | 58,451 people from Alberta Canada with incident NVAF, and no anticoagulant use. eGFR < 60 24.4%; previous stroke 10.8%; previous bleed 11.2%; age >65 52.6%; female 47%; previous MI: 11.3%; HF: 21.8%; DM: 21.6%; PVD: 3.5%; hypertensive: 64.1% | Stroke/TE (not defined) | 7340 | 2.5 years |
| McAlister, 2018[80] | CHADS2<br>CHADSVASC<br>ATRIA | This was a sample of people (of an unknown size) with AF (defined as: ICD-9CM 427.3 or ICD-10CA I48) and who were not treated with OACs. No details are given of their characteristics. They were | First TE (first stroke, TIA or systemic arterial thromboembolism) | 10,827 | 1 year |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | drawn from a larger cohort of 147,952 adult Canadians with AF. | | | |
| Olesen 2011[89] | CHADS2, CHADSVASC | 73,538 people with NVAF from Denmark. CHADSVASC of 2 or more was 80.5. Age >75 60%, female 51%, DM 9%, previous TE 18%, Vascular disease 18%, antiplatelets 35%. | Admission to hospital, or death, from TE (defined by codes I26,63,64 and 74). | unclear | 1 year |
| Olesen 2012 [88] | CHADS2with vascular disease added CHADSVASC | 924 people aged <65 years with NVAF or atrial flutter. No demographic data for these provided. | IS/thromboembolism (not defined) | 14 | Up to 10 years |
| Olesen 2012b[90] | CHADS2 CHADSVASC | 47,576 patients with atrial fibrillation (defined by ICD code I48 from Danish National Patient Registry), not on OACs. Mean age 69.4, CHF 2%, hypertension 17%, DM 2%, previous stroke 0%, vascular disease 12%, female 46.3%, aspirin 26%. 63% CHADSVASC score of 2 or more. All had CHADS2 scores of 0 or 1. | Hospitalisation or death from stroke/TE. ICD codes ICD-10: G458, G459, I63,I64,I74) | 4599 | 12 years |
| Piccini, 2013[93] | CHADS2 R2CHADS2 score – CHADS2 with creatinine clearance | Sub-group from the ATRIA cohort that were NOT taking OACS (n=16,360). No information given on | Stroke – a composite of all stroke (both ischemic and haemorrhagic) and systemic embolism. | Unclear | 3 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | incorporated (2 points for CrCl <60mL/min)<br>Sum of CrCl<60 ml and prior stroke/TIA | characteristics in Piccini, 2013. | | | |
| Schwartz, 2019[112] | Modified CHADSVASC (excluding pervious stroke/TIA) | Data from 11,443 patients with AF who were NOT on DOACs or VKAs were retrieved from the Northwestern Healthcare system's Enterprise Database Warehouse. The data allowed identification of stroke outcomes, and calculation of prior CHADSVASC scores. Mean age 67.6 for white patients and 63.1 for non-white patients. Mean CHADSVASC was 2.4 in whites and 2.2 in non-whites | Incident Stroke using ICD-9 codes and ICD-10 codes | 205 | 971 days |
| Singer 2013 [114] | ATRIA, CHADS2, CHADSVASC | 25, 306 patients with NVAF from USA. TE rate of 1.9% per year (496 stroke or other TE events). No demographic data for this cohort. | IS, defined as sudden onset of a neurologic deficit lasting >24 hours and not attributable to other causes. Other TEs: sudden occlusion to an artery to a major organ documented by imaging, surgery or pathology and not due to concomitant atherosclerosis or other causes. | 496 | 1 year |
| Siu 2014[115] | CHADS2<br>CHADSVASC | 3881 patients with NVAF (not defined) who did not receive OACs. Mean age 77, 53.5% female, 47.5% hypertensive, 18% DM, | Stroke (not defined) | 847 | 3.2 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | 1.7% renal failure on dialysis, 19% HF, 8% CAD, 1.3% PAD, 17% prior stroke/TIA. Mean CHADSVASC 3.3. | | | |
| Suzuki 2015[118] | CHADS2<br>CHADSVASC | 3588 patients with AF. Taken from 3 Japanese databases. Age 68.1, 34% female, 50% hypertension, 15% DM, 8.5% previous stroke or TIA, 15% HF, 11% CAD, 42% antiplatelet use. No data on CHADSVASC scores at baseline | Ischaemic stroke (not defined) | 69 | 1.4 years |
| Tomasdottir, 2019[121] | CHADSVASC | 231 077 (48.1% women) non-selected patients with AF not receiving oral anticoagulation from 2006 to 2014. Data from cross-linked national Swedish registers. Age 75 (men), 82 (women); HF 28.5%; hypertension 48.4%; DM 17.2%; Stroke/TIA/SE 18.7%; Vascular disease 24.1% | Ischaemic stroke | 17,540 | 2.5 years |
| Tomita 2015[122] | mCHADSVA<br>mCHADSVASC<br>CHADS2 | 294 women and 703 men with NVAF from Japan. Mean mCHADSVASC scores of 1.9 (male) and 3.3 (female). , Mean age 687% history of stroke/TIA, 58% antiplatelet use, 29% paroxysmal AF | Thromboembolic events (not defined) | 30 | 2 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| Van dem Ham 2015[124] | ATRIA, CHADSVASC and CHADS2 | 60, 594 patients with NVAF from Netherlands. Mean age 74.4 years, female 48.7%, 50% past or present smokers; 12% DM, 17.5% CHF, 54.6% hypertension, 15% previous stroke/TIA, 31% vascular disease, 28% renal dysfunction (eGFR <60 ml/min/1.73m2). | Ischeamic stroke (defined by codes in CPRD, HES or both) | 3751 | 2.1 years |
| Van Staa 2011[127] | AFI 1994<br>AFI 1998<br>ACCP 2001<br>ACCP2004<br>ACCP 2008<br>NICE 2006<br>ACC/AHA/ESC<br>CHADSVASC<br>CHADS2<br>Modified CHADS2<br>SPAF 1995<br>Hart 1999<br>Van Walraven 2002<br>Van Latum1995<br>Framingham 2003 | 79,884 patients with NVAF from Netherlands. Age 73.3, female 49.7%, 54.6% current or past smoker, CHADS score more than or equal to 3: 20%, CHF 29%, DM 17%, Hypertension 50%, previous stroke or TIA 18%. | Stroke as recorded in the GPRD, hospitalisation for stroke as recorded in the HES, and mortality resulting from stroke as recorded on death certificates. | 1233 | 4 years |
| Wang 2003[128] | Framigham<br>CHADS2<br>SPAF 1995<br>AFI 1994 | 705 participants with new onset AF from USA. Mean age 75, 48% women, 50% on hypertension therapy, | Stroke – decided by a panel of 3 Framingham investigators, including a neurologist, based on a review of all medical records and clinical data, and an examination by the neurologist. | 83 | 4 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| | | 15% DM, 18% smoking, 34% prior CHF or MI. | | | |
| Wicke, 2019[129] | CHADSVASC | A broadly representative population with AF who were not on OACs from southern Germany (n=30,299). Claims data from a statutory health insurance (AOK Baden Wuerttemberg), the largest insurance fund in the German state of Baden-Wuerttemberg (population in 2014 was 10.7 million), were used. For the year 2014, the data contained information on 3.8 million individuals, which equals to about 35% of the state's population. Age 76.4; 46.6% male; CHADSVASC score 4.25; hypertension 85%; CHF 40.2%; stroke/TIA 7.96%; DM 10.1%; | Hospitalisation for Ischaemic stroke | 961 | 2 years |
| Xing 2016[130] | CHADS2<br>CHADSVASC | 413 patients with NVAF, from China. mean age 81, 71% male, median CHADSVASC score 4.77. Hypertension 77.5%, previous stroke/TIA 36.8%, DM 36.1%, antiplatelets 68%. | Ischaemic stroke – new sudden focal neurological deficit resulting from a supposed CV cause that persisted >24 hours and not attributable to other causes. Brain imaging also used to differentiate from haemorrhage. | 59 | 2 years |

| Study | Stroke prediction tool(s) | Population (not anti-coagulated) | Outcome event definition | Number of outcome events | Follow up |
|---|---|---|---|---|---|
| Xing 2018[131] | CHADSVASC | 389 consecutive patients with AF from China. Age 83.7, 77% female, 82% hypertension, 56% vascular disease, 36% DM, 36% previous IS, 25% HF, Cr 100 mg/dL, EF 62%, CHADSVASC 4.87. | Ischaemic stroke – new sudden focal neurological deficit resulting from a supposed CV cause that persisted >24 hours and not attributable to other causes. Brain imaging also used to differentiate from haemorrhage. | 49 | 2.6 years |
| Yoshizawa 2017[133] and Komatzu, 2014[65] | R2CHADS<br>CHADS2<br>CHADSVASC | 332 people with NVAF from Japan. Age 65, male/female: 224:108, hypertension 43%, DM 13%, smoking 27%, underlying heart disease 20% (IHD 11.4%, non-ischaemic 8.6%), 18 month Hx of AF, 33% on aspirin, CHADSVASC score 2 points or more: 59%. | IS/STE. Cerebral TE confirmed based on clinical symptoms and the presence of a 3mm or larger infarct area on CT/MRI. | unclear | 4.4 years |

1

2 **Table 4: Summary of stroke/TE prediction tools and their constituent variables and cut-offs (where available)**

| Risk tool | Variables and scoring |
|---|---|
| ACC/AHA/ESC guidelines 2006 | No risk factors= low risk; age>75years, or hypertension, or heart failure, or LVEF <35%, or diabetes=intermediate risk; Previous stroke, TIA or embolism, or ≥2 moderate risk factors of (age ≥75y, hypertension, heart failure, LVEF ≤35%, diabetes)=high risk |
| ACCP (American College of Chest Physicians on Antithrombotic and Thrombolytic Therapy guidelines)2001 | No risk factors=low risk; age 65-75, or diabetes or CAD=moderate risk; age >75 years or history of ischaemic stroke/TIA, or systemic embolism or hypertension or poor left ventricular systolic function or rheumatic valve disease or prosthetic valve disease=high risk |
| ACCP 2004 | Age <65 years and no other risk factors=low risk; age 65-75 and no risk factors= moderate risk; age > 75 or history of stroke/TIA or systemic embolism or poor left ventricular function/HF or hypertension or diabetes=high risk |

| Risk tool | Variables and scoring |
|---|---|
| ACCP 2008 | No risk factors=low risk; age >75 years, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes=intermediate risk; previous stroke, TIA or embolism, or >2 moderate risk factors: age>75 years, hypertension, heart failure, LVEF <35%, diabetes=high risk |
| AFI (Atrial Fibrillation Investigators) 1994 | Age<65 years and no other risk factors=low risk; Age >65 years and no other risk factors=intermediate risk; prior ischaemic stroke or TIA, history of hypertension, history of DM = high risk |
| AFI 1998 | Risk factors: history of stroke/TIA, hypertension, diabetes.<br>Age<65 years and no other risk factors=low risk; Age >65 years and no other risk factors=intermediate risk; moderate/severe left ventricular dysfunction (echocardiography) or age <65 years and >1 risk factor or age 65-75 years and >1 risk factors or age > 75 years = high risk |
| Age modified CHADSVASC[20] | As CHADSVASC but age category for intermediate risk extended from 65-74 to 50-74. |
| ATRIA | One point each for female sex, DM, CHF, hypertension, proteinuria, eGFR<45. Age >85 = 6 points (or 9 if prior stroke/TIA), age 75-84 = 5 points (or 7 if prior stroke/TIA), age 65-74 3 points (or 7 if prior stroke/TIA), age <65 0 points (or 8 with prior stroke/TIA). |
| CHADS2 | One point each for CHF, hypertension, age 75 of older, and DM, and 2 points for prior stroke or TIA.<br>Score 0=low risk; score 1-2=intermediate risk; score 3 to 6=high risk |
| CHADS2 Alb | As CHADS2 but with addition of the albuminuria measurements only. This additional albuminuria component was categorised as low (0 points), moderate (1), or high (3). These scores were added on to the conventional CHADS2 scores (with a maximum of 6) to create this new score with a maximum of 9 (6+3) points. On this scale high risk was deemed as >2 points. |
| CHADS2 eGFR | As CHADS2 but with addition of the eGFR measurements only. This additional eGFR component was categorised as >60 mL/min/1.73m2 (0 points), 45-59 mL/min/1.73m2 (4 points), 30-44 mL/min/1.73m2 (5 points), or <30 mL/min/1.73m2 (7 points). These scores were added on to the conventional CHADS2 scores (with a maximum of 6) to create this new score with a maximum of 13 (6+7) points. On this scale high risk was deemed as >2 points. |
| CHADS2 KDIGO | As CHADS2 but with addition of the KDIGO component. KDIGO score was based on both eGFR and albuminuria measurements, and was categorised as low (0 points), moderate (3), high (5) or very high (7). These scores were added on to the conventional CHADS2 scores (with a maximum of 6) to create this new score with a maximum of 13 (6+7) points. On this scale high risk was deemed as >3 points. |
| CHADS2 with vascular disease added[88] | Vascular disease added as a risk factor to CHADS2. No details given on relationship between scores and risk. |
| CHADS2 with vWF[71] | As CHADS2, with extra point for plasma von Willebrand Factor levels (vWf) > 158 IU/dL |
| CHADSVASC 2009<br>(Also known as BIRMINGHAM) | One point for female sex, history of CHF, history of hypertension, history of vascular disease or history of DM. 2 points for history of stroke/TE. Age <65=0 points, 65-74=1 point, >75=2 points. Maximum score 9 points.<br>Low risk =0 points; 1 point=low/moderate; >2 points moderate/high |

| Risk tool | Variables and scoring |
|---|---|
| CHADSVASC with vWF[71] | As CHADSVASC, with extra point for plasma von Willebrand Factor levels (vWf) > 158 IU/dL |
| FRAMINGHAM | Age 0-10 points, female gender 6 points, systolic blood pressure 0-4 points, DM 5 points, prior stroke/TIA 6 points. Score 0-7=low risk; score 8 to 15 intermediate risk; score 16 to 31=high risk |
| GARFIELD AF Risk | Risk of ischemic stroke or systemic embolism =1-[0.991344397 exp(0.03048226*(**age**-60) + 0.952524717* history of **stroke** + 0.432357326* history of **bleed** + 0.319129628*history of **heart failure** +0.574919171*history of **chronic kidney disease** + 0.654249546*living in **Other Region (living in Aust, NZ or SA)** + 0.671380382***Black/ Mixed/ Other race** -0.582045773* **Oral Anticoagulant**)]. |
| Hart 1998 | No risk factors=low risk; hypertension+ age <75 years or diabetes=intermediate risk; history of stroke/TIA or women aged >75 years or men aged >75 years + hypertension or systolic >160=high risk |
| mCHADSVA – female gender removed [122] | As mCHADSVASC (above) but female category removed |
| mCHADSVASC – for the vascular disease criterion, only coronary artery disease is included as a risk factor [122] | As CHADSVASC but for the vascular disease component only coronary artery disease was included as a risk factor |
| Modified CHADS2[127] | Age 40-64 +1, age 65-69 +2, age 70-74 +3, age 75-79 +4, age 80-84 +5, age >85 +6, woman +1, DM +1, history of stroke/TIA +1.<br>Score 0=low risk; score 1-5 moderate risk; score 6-14 high risk |
| Modified CHADSVASC (no previous stroke/TIA)[113] | As CHADSVASC but no previous stroke/TIA component included. |
| NICE | Age <65 with no moderate/high risk factors=low risk; age >65 with no high risk factors OR age <75years with hypertension, diabetes or vascular disease = intermediate risk; previous stroke/TIA or thromboembolic event OR age >75 years with hypertension, diabetes or vascular disease OR clinical evidence of valve disease or heart failure, or impaired left ventricular function=high risk. |
| P2-CHADSVASC[77] | As CHADSVASC with addition of *abnormal p-wave axis*, which was given a score of 2 if present. |
| Q STROKE | QStroke includes measurements of age, sex, deprivation, ethnicity, body mass index, systolic blood pressure, total cholesterol:HDL cholesterol ratio, smoking status (five levels), diabetes type, congestive cardiac failure, coronary heart disease, rheumatoid arthritis, chronic kidney disease, treated hypertension, valvular heart disease, and family history of premature coronary heart disease. A % score is derived that provides an absolute risk of stroke over a choice of durations, from 1 to 10 years. |
| R2 CHADS2[3, 133 93] | R2CHADS2 was calculated by adding 2 points for renal dysfunction (i.e. estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m2); 2 points for prior stroke or TIA; and one point for each of the following factors: congestive heart failure, hypertension, age ≥ 75 and diabetes mellitus with a maximum score of 8 points. |

| Risk tool | Variables and scoring |
|---|---|
| | |
| R2 CHADS2 (71 points)[79] | This appears to be completely different to the R2 CHADS2 scheme outlined above. The score used by McAlister et al. (2017) was out of a total of 71 points, as follows: eGFR (0-29 points), previous stroke (18 points), age 65-75 (2 points), age >75 (3 points), female (5 points), previous MI (6 points), HF (-2 points), DM (4 points), Hypertension (5 points) and PVD (6 points). The authors stated that this score is normally given out of 100, but was reduced to 71 because there were no data on diastolic bp or HR, and patients had incident AF. |
| Revised CHADS2[33] | As CHADS2 risk factors but 0=low risk; 1=intermediate risk; 2to 6=high risk |
| SAMe-TT2R2 | Calculated as the sum of points after addition of one point each for female sex, age<60 years, medical history of >2 co-morbidities (among hypertension, DM, CAD or MI, PAD, CHF, previous stroke/TIA, pulmonary disease or hepatic/renal disease), and two points each for smoking and non-white race. Scores of 0-1=low risk; 2=intermediate risk; >2=high risk |
| SPAF 1999 | No risk factors=low risk; hypertension or DM = moderate risk; previous stroke/TIA or women aged >75 or men aged >75 with hypertension=high risk |
| SPAF (Stroke Prevention in Atrial Fibrillation) 1995 | No risk factors=low risk; history of hypertension=intermediate risk; prior stroke, women older than 75 years, recent clinical heart failure or LV fractional shortening <25% on echocardiography, or systolic bp >160=high risk |
| Sum of CrCl <60 mL/min and prior stroke/TIA[93] | Unclear but probably 2 points for CrCl<60mL/min and 2 points for prior stroke/TIA |
| Van Latum | Risk factors: history of stroke/TIA, IHD, enlarged cardiothoracic ratio on chest roentgenogram, systolic bp>160, AF>1 year, visible ischaemic lesion on CT.<br>No risk factors=low risk; 1-2 risk factors=moderate risk; >3 risk factors)=high risk |
| Van Walraven | No risk factors=low risk; history of stroke/TIA or treated hypertension or SBP >140 or previous MI/angina or DM=mod/high risk |

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### 3.2.11 Discrimination

**Table 5: Clinical evidence profile: Discriminative capacity of stroke prediction tools featured in the studies (see table 3).**

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| CHADS2 | 26 | 572,597 (one study n is unknown) | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | No serious imprecision | **POOLED EFFECT: Random Effects: 0.68(0.65-0.70); $I^2$=98%** | VERY LOW |
| Modified CHADS2 (Van Staa, 2010) | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.69(0.67-0.71) | VERY LOW |
| Revised CHADS2 (Friberg 2012) | 2 | 91,574 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | **POOLED EFFECT: Fixed Effects: 0.62(0.61-0.63); $I^2$=0%** | LOW |
| R2 CHADS2 (Abumaileq 2015, Yoshizawa, 2017, Piccini, 2013) | 3 | 16846 | Very serious risk of bias[a] | Very serious risk of inconsistency[b] | No serious indirectness | Serious imprecision | **POOLED EFFECT: Random Effects: 0.74(0.62-0.86); $I^2$=92%** | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| R2CHADS2 (71 points) (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.66(0.64-0.67) | LOW |
| CHADS2 KDIGO (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.65(0.64-0.66) | LOW |
| CHADS2 Alb (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.65(0.64-0.67) | LOW |
| CHADS2 eGFR (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.67(0.65-0.68) | LOW |
| CHADS2 with vWF | 1 | 994 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.69(0.60-0.77) | VERY LOW |
| CHADSVASC 2009 | 26 | 674,678 (in one study n unknown) | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | No serious imprecision | **POOLED EFFECT: Random Effects: 0.68(0.65-0.70); $I^2$=99%** | VERY LOW |
| P2-CHADSVASC | 2 | 2929 | Very serious | No serious inconsistency | No serious indirectness | Serious imprecision | **POOLED EFFECT: Fixed effect 0.68 (0.62-0.75) $I^2$=0%** | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | risk of bias[a] | | | | | |
| Age modified CHADSVASC (Chao 2016) | 1 | 124,271 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.71(0.70-0.71) | MODERATE |
| mCHADSVASC (modified in Tomita 2015) | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.60(0.51-0.68) | LOW |
| Modified CHADSVASC (no stroke/TIA)[108] | 1 | 11433 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.65(0.57-0.72)(non-white)<br>0.68(0.64-0.72)(white) | VERY LOW |
| mCHADSVA – (Modified in Tomita 2015) | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.62(0.53-0.71) | VERY LOW |
| Q STROKE | 1 | 7689 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.65(0.62-0.67) [Female]<br>0.71(0.69-0.73)[Male] | LOW |
| ATRIA | 6 | 259,658 (one study | Very serious | Very serious | No serious indirectness | serious imprecision | **POOLED EFFECT: Random Effects: 0.70 (0.67-0.74); $I^2$=99%** | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | unknown n) | risk of bias[a] | inconsistency | | | | |
| AFI 1994 | 7 | 182,064 | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | No serious imprecision | **POOLED EFFECT: Random Effects: 0.62(0.57-0.66); $I^2$=92%** | VERY LOW |
| AFI 1998 | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.61(0.60-0.62) | LOW |
| SPAF 1995 | 5 | 90,490 | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | Serious imprecision | **POOLED EFFECT: Random Effects: 0.68(0.58-0.79); $I^2$=97%** | VERY LOW |
| SPAF 1999 | 2 | 91,574 | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Very serious imprecision[c] | **POOLED EFFECT: Random Effects: 0.60(0.49-0.70); $I^2$=50%** | VERY LOW |
| FRAMINGHAM | 6 | 180331 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | **POOLED EFFECT: Fixed Effects: 0.67(0.66-0.67); $I^2$=43%** | LOW |
| ACCP 2001 | 2 | 82,464 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | **Range:0.58 to 0.62**<br>**Median: 0.60** | LOW |
| ACCP 2004 | 2 | 85,472 | Very serious | No serious inconsistency | No serious indirectness | No serious imprecision | **Range: 0.60 to 0.61**<br>**Median: 0.605** | LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | risk of bias[a] | | | | | |
| ACCP 2008 | 2 | 80,968 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | **POOLED EFFECT: Fixed Effects: 0.64(0.62-0.66); $I^2$=0%** | LOW |
| ACC/AHA/ESC guidelines 2006 | 3 | 171,458 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | **POOLED EFFECT: Fixed Effects: 0.62(0.61-0.63); $I^2$=47%** | LOW |
| NICE | 3 | 171,458 | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | **POOLED EFFECT: Random Effects: 0.62(0.59-0.65); $I^2$=72%** | VERY LOW |
| Hart 1998 | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.62(0.60-0.64) | LOW |
| Van Walraven | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.55(0.54-0.58) | LOW |
| Van Latum | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.57(0.55-0.59) | LOW |
| CHADSVASC with vWF | 1 | 994 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.68(0.59-0.76) | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| GARFIELD | 1 | 2301 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.70(0.63-0.77) | VERY LOW |
| SAMe-TT2R2 | 1 | 3483 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | 0.51(0.49-0.53) | LOW |
| Sum of CrCl <60 mL/min and prior stroke/TIA[88] | 1 | 16,360 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.61 (0.58-0.64) | LOW |

*Pooling (meta-analysis) was carried out if there were at least two studies per risk tool with confidence intervals. RevMan was used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*
*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*
*b) Where data were pooled, an $I^2$ of 50-74% was deemed serious inconsistency and an $I^2$ of 75% or above was deemed very serious inconsistency. If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more Cis did not overlap then a rating of serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences. Clinically the studies appeared reasonably homogeneous, with similar rates of hypertension, diabetes and former stroke.*
*c) The judgement of precision was based on the spread of confidence interval across two clinical thresholds: C statistics of 0.5 and 0.7. The threshold of 0.5 marked the boundary between no predictive value better than chance and a predictive value better than chance. The threshold of 0.7 marked the boundary above which the committee might consider recommendations. If the 95% Cis crossed one of these thresholds a rating of serious imprecision was given and if they crossed both of these thresholds a rating of very serious imprecision as given.*

**Table 6: Clinical evidence profile: sensitivity and specificity of stroke prediction tools featured in the studies (see table 3). For pooled data the 95% CIs of individual studies can be found in the Forest plots in the appendices. For individual or non-pooled data the 95% CIs are given below. The pooled sensitivity/specificity values have been calculated using Bayesian methodology and are expressed as medians (95% credible intervals).**

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| CHADS2 at threshold of ≥1 | 6 | 172,747 | **Pooled sensitivity: 0.874(0.676-0.960)** | **Pooled specificity: 0.228(0.131-0.501)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADS2 at threshold of ≥2 | 5 | 165,058 | **Pooled sensitivity: 0.582(0.308-0.811)** | **Pooled specificity: 0.625(0.363-0.835)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | risk of bias[a] | | | | |
| CHADS2 at threshold of ≥3 | 5 | 165,058 | **Pooled sensitivity: 0.316(0.129-0.593)** | **Pooled specificity: 0.845(0.641-0.944)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | VERY LOW |
| Revised CHADS2 (Friberg 2012) | 1 | 90,490 | 0.980 at standard threshold [no raw data in paper, and no 95% CIs reported] | 0.150 at standard threshold [no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| R2CHADS2 (71 points) (McAlister, 2017) | 1 | 7340 | 0.800 no specified threshold | 0.511 no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADS2 KDIGO (McAlister, 2017) | 1 | 7340 | 0.726 no specified threshold | 0.575 no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADS2 Alb (McAlister, 2017) | 1 | 7340 | 0.821 no specified threshold | 0.488 no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADS2 eGFR (McAlister, 2017) | 1 | 7340 | 0.693 no specified threshold | 0.640 no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADSVASC 2009 at threshold of ≥1 | 9 | 440,691 | **Pooled sensitivity: 0.977(0.947-0.992)** | **Pooled specificity: 0.092(0.051-0.156)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADSVASC 2009 at threshold of ≥2 | 9 | 438983 | **Pooled sensitivity: 0.923(0.850-0.964)** | **Pooled specificity: 0.223(0.144-0.328)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | VERY LOW |
| CHADSVASC 2009 at threshold of ≥3 | 8 | 569,938 | **Pooled sensitivity: 0.809(0.631-0.913)** | **Pooled specificity: 0.431(0.287-0.582)** | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADSVASC 2009 at threshold of ≥4 | 8 | 438,829 | **Pooled sensitivity: 0.524(0.347-0.695)** | **Pooled specificity: 0.646(0.477-0.781)** | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| Modified CHADSVASC (no | 1 | 11,433 | 0.821(0.759-0.872) | 0.393(0.384-0.402) | **Sensitivity** | | | | |
| | | | | | Very serious | NA | No serious indirectness | No serious imprecision | LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| stroke/TIA)[113] at threshold for risk of ≥2 | | | | | risk of bias[a] | | | | |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| Modified CHADSVASC (no stroke/TIA)[113] at threshold for risk of ≥3 | 1 | 11,433 | 0.631(0.559-0.699) | 0.612(0.603-0.621) | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | Serious imprecision | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| Modified CHADSVASC (no stroke/TIA)[113] at threshold for risk of ≥4 | 1 | 11,433 | 0.359(0.292-0.431) | 0.798(0.791-0.805) | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | 1 | 7689 | | | **Sensitivity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Q STROKE with optimal cut-off at top 63% | | | 0.825 (0.798-0.849) with optimal cut-off at top 63% | 0.395(0.383-0.407) with optimal cut-off at top 63% | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 90% | 1 | 7689 | 0.992(0.984-0.997) with cut-off at top 90% | 0.112(0.105-0.119) with cut-off at top 90% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 85% | 1 | 7689 | 0.979(0.967-0.987) with cut-off at top 85% | 0.167(0.158-0.176) with cut-off at top 85% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 80% | 1 | 7689 | 0.958(0.943-0.971) with cut-off at top 80% | 0.221(0.211-0.231) with cut-off at top 80% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 70% | 1 | 7689 | 0.890(0.868-0.909) with cut-off at top 70% | 0.325(0.314-0.336) with cut-off at top 70% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | Serious imprecision[c] | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| ATRIA at threshold for risk of ≥1 | 2 | 158004 | **Median[d]: 0.985(0.983-0.987)** | **Median[d]: 0.091(0.089-0.168)[10]** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | Serious imprecision[c] | VERY LOW |
| ATRIA at threshold for risk of ≥2 | 1 | 152149 | 0.967(0.964-0.970) | 0.166(0.164-0.168) | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious | NA | No serious indirectness | No serious imprecision | LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | risk of bias[a] | | | | |
| ATRIA at threshold for risk of ≥3 | 1 | 152149 | 0.958(0.955-0.962) | 0.192(0.189-0.194) | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| ATRIA at threshold for risk of ≥4 | 1 | 152149 | 0.936(0.931-0.940) | 0.241(0.238-0.243) | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| ATRIA at threshold for risk of ≥5 | 1 | 152149 | 0.894(0.888-0.899) | 0.309(0.307-0.312) | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious | NA | No serious indirectness | No serious imprecision | LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | risk of bias[a] | | | | |
| ATRIA at threshold for risk of ≥6 | 3 | 158158 | **Median[d]: 0.444(0.137-0.788)** | **Median[d]: 0.510(0.426-0.594)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency | No serious indirectness | Serious imprecision[c] | VERY LOW |
| ATRIA at threshold for risk of ≥7 | 2 | 152303 | **Median[d]: 0.444(0.137-0.788)** | **Median[d]: 0.607(0.522-0.687)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | LOW |
| AFI 1994 | 1 | 90,490 | 0.990 at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.090 at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| SPAF 1999 | 1 | 90,490 | 0.890 at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.290 at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| FRAMINGHAM | 1 | 90,490 | 0.920 at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.260 at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| ACC/AHA/ESC guidelines 2006 | 1 | 90,490 | 0.980 at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.150 at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| NICE | 1 | 90,490 | 1.000 at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.090 at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |

*Pooling (meta-analysis) was carried out if there were at least three studies per risk tool with confidence intervals. RevMan and WinBugs were used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*

*a) Risk of bias was assessed using the PROBAST checklist. Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) Where data were pooled, inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.*

*c) Imprecision was assessed based on inspection of the confidence region in the meta-analysis or, where meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60 for sensitivity and 0.5 and 0.1 for specificity), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.*

*d)For unpooled data the median value was given (of data with 95% CIs). If there were an even number of data points in the unpooled data, the data point chosen in the central pair was the one with lower sensitivity, with its paired specificity.*

## Additional discrimination measures – D statistic

**Table 7: Clinical evidence profile: D statistics of prediction tools featured in the studies (see table 3)**

| Risk tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | D statistic (95%CI) | Quality |
|---|---|---|---|---|---|---|---|---|
| Q Stroke [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.820(0.660-0.990) [Female] | MODERATE |
| Q Stroke [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 1.150(1.000 to 1.300) [Male] | LOW |
| CHADS2 [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.640(0.490-0.810) [Female] | MODERATE |
| CHADS2 [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.810(0.660 to 0.960) [Male] | MODERATE |
| CHADSVASC [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.670(0.510-0.830) [Female] | MODERATE |
| CHADSVASC [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 0.970(0.820 to 1.120) [Male] | LOW |

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for most risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the Framingham risk tool because the study concerned also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) The judgement of precision was based on the spread of confidence intervals around the clinically important point at 1.1. If the CIs crossed 1.1 then they were graded as seriously imprecise.*

### 3.2.21 Calibration

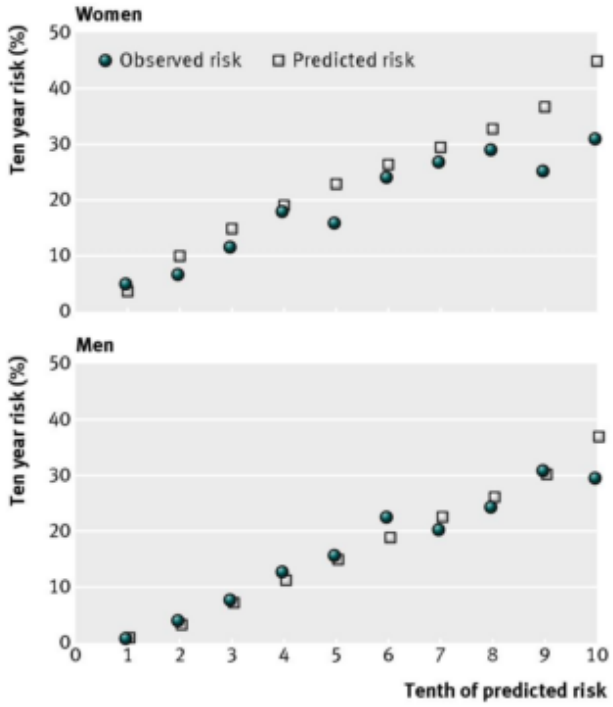
2 **Table 8: Clinical evidence profile: calibration statistics of prediction tools featured in the studies (see table 3)**

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | $R^2$ (95%CI) | Hosmer-Lemeshow statistics | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Q Stroke [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.140(0.092-0.187)[Female] | - | MODERATE |
| Q Stroke [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.241(0.193-0.289)[Male] | - | MODERATE |
| CHADS2 [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.091(0.049-0.132)[Female] | - | MODERATE |
| CHADS2 [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.135(0.091-0.179) [Male] | - | MODERATE |
| CHADSVASC [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.096(0.055-0.138)[Female] | - | MODERATE |
| CHADSVASC [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.183(0.137-0.228) [Male] | - | MODERATE |
| Framingham | 1 | 705 | Very serious risk | No serious inconsistency | No serious indirectness | NA | - | 7.6 (values <20 indicate good calibration. No CIs or p value provided in study. | LOW |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | of bias[a] | | | | | | | |

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for most risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the Framingham risk tool because the study concerned also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*
*b) The judgement of precision was based on the spread of confidence intervals around the clinically important point at 0.5. If the CIs crossed 0.5 then they were graded as seriously imprecise.*

The figure below shows there is good calibration of Q stroke with observed risk[46], with close agreement between predicted and observed risk of stroke across all 10ths of risk.




Data from QResearch database version 34, all patients free of free of stroke or transient ischaemic attack

**Fig 2** Mean predicted risks and observed risk of stroke or transient ischaemic attack at 10 years by tenth of predicted risk applying the QStroke risk prediction scores to the subset of patients with atrial fibrillation.

P2-CHADSVASC was well-calibrated in the ARIC cohort but less so in the MESA cohort in the study by Maheswari, 2019 [77]

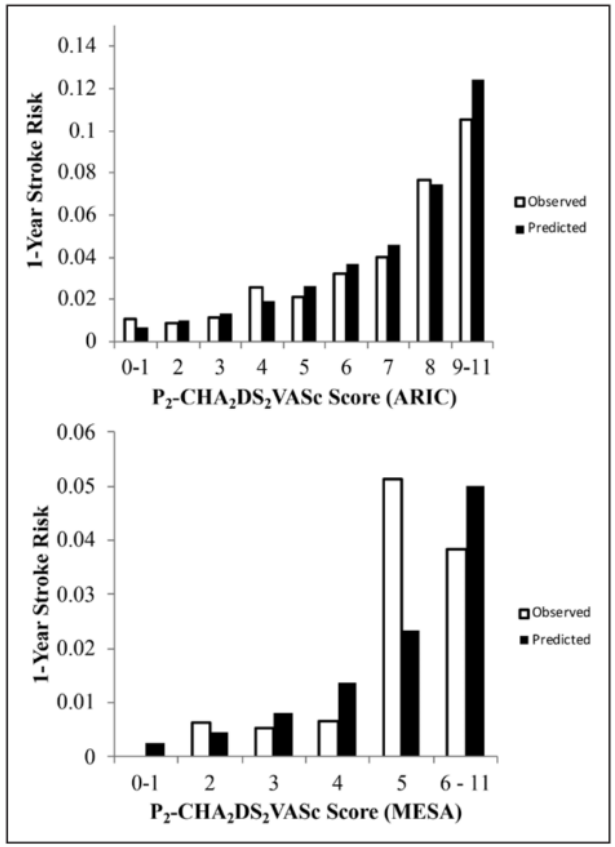



**Figure 2. Calibration of the $P_2$-$CHA_2DS_2VASc$ score in ARIC and MESA.** Observed (white bars) and predicted (black bars) 1-year stroke risk for $P_2$-$CHA_2DS_2$-VASc score categories in the ARIC study (Atherosclerosis Risk in Communities) and the MESA (Multi-Ethnic Study of Atherosclerosis).

1

### 3.2.31 Reclassification

2 Several studies reported the Net Reclassification Improvement (NRI). This is expressed in terms of one (index) risk tool to another
3 (comparator) risk tool and gives a score between -2 and +2 (with +2 representing the best possible performance of the index tool relative to
4 the comparator, and -2 the worst). The score represents the net improvement of the index test relative to the comparator in terms of the
5 proportion of true cases (judged by later development of stroke/TE) that are correctly up-classified by the tool (relative to any false negative
6 classifications yielded by the comparator), and the proportion of false cases (judged by the lack of later stroke/TE) that are correctly down-
7 classified by the tool (relative to any false positive classifications yielded by the comparator). Meanwhile, incorrect up-classification or incorrect
8 down-classification of the index relative to the comparator convey negative scores to the NRI, and so if a score is negative overall this
9 indicates the index is less accurate than the comparator.

10 NRI data are given below for each risk tool comparison. The data have been divided into two tables, by comparator.

11 **Table 9: Clinical evidence profile: NRI of prediction tools featured in the studies (see table 3) with CHADS2 as the comparator**

| Prediction tool comparison | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | [NRI(95% CI)](95%CI) | Quality |
|---|---|---|---|---|---|---|---|---|
| ATRIA versus CHADS2 | 4 | 259,504 | Very serious risk of bias[a] | Very serious inconsistency[b] | No serious indirectness | No serious imprecision | -0.0<br>**POOLED EFFECT: Random effects NRI +0.130 (+0.050 to +0.220); $I^2$=98%** | VERY LOW |
| R2CHADS2 (71 point) versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.015 (-0.036 to 0.006) | VERY LOW |
| R2CHADS2 versus CHADS2 | 1 | 16,360 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.226(0.125 to 0.307) | LOW |
| CHADS2 KDIGO | 1 | 58,451 | Very serious | No serious inconsistency | No serious indirectness | No serious imprecision | -0.026(-0.049 to -0.002) | LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| versus CHADS2 | | | risk of bias[a] | | | | | |
| CHADS2 Alb versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.018 (-0.026 to 0.028) | VERY LOW |
| CHADS2 eGFR versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | +0.006 (-0.017 to 0.030) | VERY LOW |
| CHASDS2 with vascular disease versus CHADS2 | 1 | 2002 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | +0.400 (0.000 to +0.800) | MODERATE |

*Pooling (meta-analysis) was carried out if there were at least two studies per risk tool with confidence intervals. RevMan was used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) Where data were pooled, an $I^2$ of 50-74% was deemed serious inconsistency and an $I^2$ of 75% or above was deemed very serious inconsistency. If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more Cis did not overlap then a rating of serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences. Clinically the studies appeared reasonably homogeneous, with similar rates of hypertension, diabetes and former stroke.*

*c) The judgement of precision was based on the spread of confidence intervals. If the lower 95% CI passed across 0 then this was graded as seriously imprecise*

**Table 10: Clinical evidence profile: NRI of prediction tools featured in the studies (see table 3) with CHADSVASC (or CHADSVASC derivatives) as the comparator**

| Prediction tool comparison | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | [NRI(95% CI)](95%CI) | Quality |
|---|---|---|---|---|---|---|---|---|
| ATRIA versus CHADSVASC | 3 | 210,053 | Very serious risk of bias[a] | Very serious inconsistency[b] | No serious indirectness | No serious imprecision | to 0.300)[114] **POOLED EFFECT: Random effects NRI +0.230 (+0.200 to +0.250); $I^2$=79%** | VERY LOW |
| Age-modified CHADSVASC versus CHADSVASC | 1 | 124,271 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | +0.039 (0.0216 to 0.0459) | MODERATE |
| CHADS2 versus CHADSVASC | 8 | 210,854 | Very serious risk of bias[a] | Very serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | )[130] **POOLED EFFECT: Random effects NRI -0.020 (-0.060 to +0.020); $I^2$=84%** | VERY LOW |
| Revised CHADS2 versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.070 | LOW |
| Framingham versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.120 | LOW |
| SPAF 1999 versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.120 | LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ACC/AHA/ESC versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.070 | LOW |
| NICE versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.000 | LOW |
| AFI 1994 versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.000 | LOW |
| CHADS2 versus mCHADSVASC | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.100(-0.280 to 0.080) | VERY LOW |
| CHADS2 versus mCHADSVA | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.030 (-0.210 to 0.160) | VERY LOW |
| mCHADSVASC versus mCHADSVA | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | +0.110(0.010 to 0.200) | LOW |
| P2-CHADSVASC versus CHADSVASC | 2 | 2929 | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | **POOLED EFFECT: Random effects NRI +0.330 (+0.100 to +0.570); $I^2$=53%** | VERY LOW |

*Pooling (meta-analysis) was carried out if there were at least two studies per risk tool with confidence intervals. RevMan was used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) Where data were pooled, an $I^2$ of 50-74% was deemed serious inconsistency and an $I^2$ of 75% or above was deemed very serious inconsistency. If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more Cis did not overlap then a rating of*

*serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences. Clinically the studies appeared reasonably homogeneous, with similar rates of hypertension, diabetes and former stroke.*
*c) The judgement of precision was based on the spread of confidence intervals. If the lower 95% CI passed across 0 then this was graded as seriously imprecise*

**Q Stroke versus CHADSVASC**

Data relevant to classification were given in one study[46], but there was insufficient information on true events and non-events to allow calculation of the NRI

**Q Stroke versus CHADS2**

Data relevant to classification were given in one study[46], but there was insufficient information on true events and non-events to allow calculation of the NRI

**Sum of CrCL <60mL/min and prior stroke/TIA** versus **R2CHADS 2**
+0.024 (-0.077 to + 0.029)[93]

# 3.3 Economic evidence

## 3.3.1 Included studies

No relevant health economic studies were identified.

## 3.3.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

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

# 4 The committee's discussion of the evidence

## 4.1 Interpreting the evidence

### 4.1.1 The outcomes that matter most

The committee agreed that the most critical accuracy data for decision-making were sensitivity/specificity, net reclassification improvement (NRI), and calibration data. Sensitivity and specificity measures for specific thresholds were deemed useful outcomes, because they allow for the differing importance placed on sensitivity or specificity, and are specific to clinically relevant thresholds of risk. Reclassification measures were also favoured because they are sensitive to small changes in a tool, such as an additional parameter contributing to the score. Calibration measures were deemed the most useful outcome, however, because they give the most realistic impression of how well a tool predicts the actual risk of the event at a particular test threshold. Unfortunately, because these measures were unavailable for many tools they played a smaller part than anticipated in decision-making.

C statistics data were deemed important, but less critical than the other outcomes, because they do not take the relative importance of sensitivity and specificity into account. For example, tool A may have a higher C statistic than tool B, but this superior C statistic may be because tool A tends towards very high overall specificity, even though its overall sensitivity may be inferior to that of tool B. If sensitivity is deemed the more important aspect of predictive accuracy, then the C statistic may be a misleading measure in this context. In addition, C statistics effectively measure the overall accuracy at *all* risk thresholds defined by a tool (quantified by the area under the curve described by sensitivity and 1-specificity co-ordinates at each possible risk threshold). In practice, however, a test will be used at a specific threshold, relating to the point where risk is deemed to change from an acceptable to an unacceptable risk, and so the overall accuracy at all thresholds, including clinically non-relevant ones, may be misleading. Finally, C-statistics are insensitive to small changes in the risk model (when new prognostic factors are added to an existing model). Nevertheless, the committee included the C statistic as an outcome as it gives a general measure of a tool's ability to differentiate between high and low risk patients, and is commonly reported in these studies.

The committee confirmed that the recommendations on anticoagulation applied to all patients with AF irrespective of whether they were symptomatic, to all categories of AF (paroxysmal, persistent and permanent), to patients following cardioversion considered at continuing risk of arrhythmia recurrence, and to patients with atrial flutter.

### 4.1.2 The quality of the evidence

Evidence was generally deemed low or very low quality. Risk of bias was serious or very serious due to unclear methodology in terms of blinding of risk tool and outcome data, and in many studies the follow up time was short (<5 years) or involved few events (<100). The quality was also affected by serious or very serious heterogeneity.

### 4.1.3 Benefits and harms

Sub-optimal predictive accuracy can lead to two harms, in the context of predicting stroke in people with AF. Sub-optimal accuracy caused by low sensitivity will lead to more people having strokes or thromboembolic events because they are incorrectly deemed to be at too low a level of risk to be prescribed anticoagulants. Sub-optimal accuracy caused by low

specificity will lead to more people having unnecessary bleeding episodes or other side-effects of anticoagulants because they have been prescribed anticoagulants when their risk of stroke is actually low.

The judgement of which is the most important harm depends on the severity of these harms and also their probability of occurring. Scoring systems generally have a trade-off between sensitivity and specificity. The committee agreed that the greater emphasis should be on avoiding strokes because bleeding events were both less probable than strokes and also less likely to have such serious consequences as strokes if they occurred. This was judged to be particularly so given the new generation of anticoagulants: non-vitamin K antagonist oral anticoagulants (DOACs). Thus tools favouring sensitivity were preferred. However it was also recognised that it is easy to design a perfectly sensitive test if specificity is not considered at all (for example, simply giving anticoagulants to all people with AF is equivalent to the use of a perfectly sensitive but completely non-specific test). It was recognised that the ideal tool would have high sensitivity but also have enough specificity to allow the people with lowest risk to avoid unnecessary anticoagulation, with the excess risk that would entail.

The CHADS2 was similar to the CHADSVASC in terms of the C statistic, but it was felt too insensitive at even the lowest thresholds to be able to rival the CHADSVASC. However, there were two new tools that were regarded as potential rivals to the CHADSVASC in terms of predictive accuracy: the Q stroke and ATRIA.

The Q stroke was viewed as highly promising, as it had excellent sensitivity and reasonable specificity at the 85$^{th}$ percentile of scores. The D statistic point estimates of the Q stroke were numerically superior to those in the CHADSVASC, with the Q stroke values in men suggesting a clinically important degree of discrimination. However, there was some overlap of 95% confidence intervals between Q stroke and CHADSVASC suggesting that these differences could be explained by sampling error. There was also good calibration of the Q stroke at lower risks, particularly in men, and the $R^2$ data were again numerically superior to the CHADSVASC, although again the overlap of 95% confidence intervals suggested that sampling error could be a factor. However the available data were based on only one derivation/validation study. The study contained a separate sample for the validation analysis but the committee noted that despite the obvious potential of this tool, a single study was insufficient to inform recommendations, and that further work in other AF samples was required before this tool could be recommended over the CHADSVASC.

The ATRIA was also regarded as an excellent tool, with a C statistic that was higher than the CHADSVASC. It also had a significantly better NRI compared to the CHADSVASC. However this was largely due to down-classification of non-events. Accordingly, this was accompanied by better specificity but lower sensitivity (around 0.80+) than the CHADSVASC (around 0.90+) at standard thresholds (threshold of $\geq$2 for CHADSVASC and $\geq$6 for ATRIA). At lower ATRIA thresholds the sensitivity/specificity profile of ATRIA was very similar to CHADSVASC (at CHADSVASC thresholds of $\geq$1 or $\geq$2) but did not become any better than it. The decision of the committee was therefore that CHADSVASC was slightly more useful because of its better ability to ensure that people truly at risk of stroke were anticoagulated.

In addition to ATRIA having potentially more harms than CHADSVASC in terms of ATRIA leading to more people at risk of stroke not being anticoagulated, the ATRIA was also believed to be more difficult to use. The committee discussed the time delays in getting a dip-stick assessment of proteinuria done and retesting eGFR for the ATRIA, although it was pointed out that ATRIA might, on occasions, be able to utilise data already in the patients' notes rather than requiring the acquisition of new data.

Thus CHADSVASC was regarded as the best available tool. The ideal threshold for the CHADSVASC in terms of anticoagulation was agreed to be $\geq$2, as this gave an excellent

compromise between high sensitivity and reasonable specificity. This fitted with current practice. The reviewed data did not allow the committee to decide if men and women should have different thresholds.

### 4.1.4 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review. The committee discussed the different resource use for the different tests, in particular ATRIA compared to CHADSVASC. It was noted that testing proteinuria for ATRIA required a urine dipstick test. This can be particularly challenging with older frail patients who may require assistance to provide a urine sample and therefore may incur additional cost over CHADVASC. In addition, further blood tests would be needed for ATRIA as the eGFR would need repeating. The committee noted that these additional tests would create delays and disruption to clinics.

The committee also discussed the potential harm associated with ATRIA compared to CHADSVASC, in terms of ATRIA leading to more people at risk of stroke not being anticoagulated (as a result of the lower sensitivity). The committee noted that this harm would likely make ATRIA less cost-effective than CHADSVASC due to the high cost of a stroke to the NHS and detrimental impact on QALYs. This would likely outweigh the increased anticoagulation as a result of the lower specificity of CHADSVASC. Health economic modelling of ATRIA compared to CHADSVASC was not prioritised by the guideline committee as other areas of the guideline were considered to have a greater potential resource impact (ablation and anticoagulation).

The committee agreed that there was not sufficient clinical evidence of superiority for ATRIA to warrant a change in practice and the potential harms and costs associated with this new tool.

### 4.1.5 Other factors the committee took into account

Patient views are central when considering the trade-off between the benefits and harms. The committee agreed that it is important to ensure that information and education are provided to ensure the benefits and harms are fully understood (see the NICE patient experience guideline).

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# Appendices

# Appendix A: Review protocols

**Table 11: Review protocol: What is the most clinically and cost-effective risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation?**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | [Complete this section with the PROSPERO registration number once allocated] |
| 1. | Review title | Clinical and cost-effectiveness of tools for assessing stroke risk in people with atrial fibrillation |
| 2. | Review question | What is the most clinically and cost-effective risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation? |
| 3. | Objective | To identify the most clinically and cost effective tool to measure the risk of stroke and thromboembolic complications in this population |
| 4. | Searches | The following databases will be searched:<br>Cochrane Central Register of Controlled Trials (CENTRAL)<br>Cochrane Database of Systematic Reviews (CDSR)<br>Embase<br>MEDLINE<br><br>Searches will be restricted by:<br>English language<br>Human studies<br>Letters and comments are excluded.<br><br>Other searches:<br>Inclusion lists of relevant systematic reviews will be checked by the reviewer.<br><br>The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| 5. | Condition or domain being studied | Atrial Fibrillation |
| 6. | Population | Inclusion:<br>People aged over 18 with AF.<br>Exclusion:<br>People with AF due to severe valvular disease |
| 7. | Intervention/Exposure/Test | Any stroke risk tool (for example, ABC stroke score, Q stroke, ATRIA, Troponin 2, CHADS2).<br>Any version of CHADS2VASC with modifications |

| ID | Field | Content |
|---|---|---|
| | | [Note: treat each test using a different threshold as a separate intervention; for example, Q stroke using the threshold of X for 'need for anticoagulation' is treated as a separate intervention to Q stroke using the threshold of Y for 'need for anticoagulation']. |
| 8. | Comparator/Reference standard/Confounding factors | CHADS2VASC (the established method, as recommended by previous version of this guideline) |
| 9. | Types of study to be included | Systematic reviews<br>RCTs (including those with a cross-over design).<br><br>Non-randomised studies will be excluded. |
| 10. | Other exclusion criteria | Non-English language studies.<br>Abstracts will be excluded as it is expected there will be sufficient full text published studies available. |
| 11. | Context | N/A |
| 12. | Primary outcomes (critical outcomes) | health-related quality of life<br>mortality<br>stroke or thromboembolic complications<br>major bleeding<br><br>Longest follow up point always used |
| 13. | Secondary outcomes (important outcomes) | None |
| 14. | Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion.<br>The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.<br><br>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.<br><br>A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary). |

| ID | Field | Content | |
|---|---|---|---|
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>For Intervention reviews the following checklist will be used according to study design being assessed:<br>Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>Randomised Controlled Trial: Cochrane RoB (2.0)<br><br>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. | |
| 16. | Strategy for data synthesis | Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.<br>Heterogeneity between the studies in effect measures will be assessed using the $I^2$ statistic and visually inspected. We will consider an $I^2$ value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects.<br><br>GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.<br><br>Publication bias is tested for when there are more than 5 studies for an outcome.<br>Other bias will only be taken into consideration in the quality assessment if it is apparent.<br><br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.<br><br>If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis. | |
| 17. | Analysis of sub-groups | Stratification<br>None<br><br>Sub-grouping<br>If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies:<br>None | |
| 18. | Type and method of review | ☐ | Intervention |
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |

| ID | Field | Content | | |
|---|---|---|---|---|
| | | ☐ | Service Delivery | |
| | | ☒ | Other (please specify): RCT review of prediction tools | |
| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | | | |
| 22. | Anticipated completion date | | | |
| 23. | Stage of review at time of this submission | Review stage | Started | Completed |
| | | Preliminary searches | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Formal screening of search results against eligibility criteria | ☐ | ☑ |
| | | Data extraction | ☐ | ☑ |
| | | Risk of bias (quality) assessment | ☐ | ☑ |
| | | Data analysis | ☐ | ☑ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | | |
| 25. | Review team members | From the National Guideline Centre:<br>Sharon Swain<br>Mark Perry<br>Nicole Downes<br>Sophia Kemmis Betty<br>Elizabeth Pearton | | |
| 26. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. | | |

| ID | Field | Content | |
|---|---|---|---|
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. | |
| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage]. | |
| 29. | Other registration details | | |
| 30. | Reference/URL for published protocol | | |
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts<br>issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. | |
| 32. | Keywords | Atrial Fibrillation, stroke prediction tools | |
| 33. | Details of existing review of same topic by same authors | N/A | |
| 34. | Current review status | ☒ | Ongoing |
| | | ☐ | Completed but not published |
| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 35.. | Additional information | N/A | |
| 36. | Details of final publication | www.nice.org.uk | |

**Table 12: Review protocol: What is the most accurate risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation?**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | Not registered |

| ID | Field | Content |
|---|---|---|
| 1. | Review title | Accuracy of risk stratification tools for predicting stroke or thromboembolic events in people with atrial fibrillation. |
| 2. | Review question | What is the most accurate risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation? |
| 3. | Objective | To identify the most accurate tool to measure the risk of stroke or any thromboembolic event in this population. |
| 4. | Searches | The following databases will be searched:<br>Cochrane Central Register of Controlled Trials (CENTRAL)<br>Cochrane Database of Systematic Reviews (CDSR)<br>Embase<br>MEDLINE<br><br>Searches will be restricted by:<br>English language<br><br>Other searches:<br>None<br><br>The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| 5. | Condition or domain being studied | Atrial Fibrillation |
| 6. | Population | People aged over 18 with a diagnosis of AF who are not being anticoagulated.<br>Exclusion: People who are already being anticoagulated |
| 7. | Index Test | Any stroke risk tool (e.g ABC stroke score, Q stroke, ATRIA, Troponin 2, CHADSVASC)<br>Any other version of CHADSVASC with modifications |
| 8. | Comparator/Reference standard/Confounding factors | Later stroke or thromboembolic event |
| 9. | Types of study to be included | Prognostic prediction tool evaluation studies. |
| 10. | Other exclusion criteria | Non-English language studies. |
| 11. | Context | N/A |
| 12. | Primary outcomes (critical outcomes) | Simple diagnostic (prognostic) accuracy outcomes, such as sensitivity and specificity<br>C statistic (based on sensitivity and specificity but useful if >1 threshold used).<br>Calibration outcomes<br>Reclassification – scored from -2 (worst) to +2 (best), and based on the degree of correct (+1 for each) and incorrect (-1 for each) up- |

| ID | Field | Content | | |
|---|---|---|---|---|
| | | classifications and down-classifications of one test relative to another test, using the outcome of stroke or thromboembolic events as reference. | | |
| 13. | Secondary outcomes (important outcomes) | None | | |
| 14. | Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br>The full text of these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above.<br>A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4).<br>Data extraction will be independently quality assured by a second reviewer, discrepancies will be identified and resolved through discussion (with a third party where necessary). | | |
| 15. | Risk of bias (quality) assessment | Risk of bias quality assessment will be assessed using PROBAST.<br>Assessment will be independently quality assured by a second reviewer. Disagreements between the reviewers will be resolved by discussion, with involvement of a third party where necessary. | | |
| 16. | Strategy for data synthesis | Where possible C statistic and NRI data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in RevMan. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed using I2 thresholds.<br>If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables. | | |
| 17. | Analysis of sub-groups | If heterogeneity is identified, where data is available, subgroup analysis will be carried out for the following subgroups:<br>None | | |
| 18. | Type and method of review | ☐ | Intervention | |
| | | ☐ | Diagnostic | |
| | | ☒ | Prognostic | |
| | | ☐ | Qualitative | |
| | | ☐ | Epidemiologic | |
| | | ☐ | Service Delivery | |
| | | ☐ | Other (please specify) | |
| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | | | |
| 22. | Anticipated completion date | | | |
| 23. | | Review stage | Started | Completed |

| ID | Field | Content | | |
|---|---|---|---|---|
| | Stage of review at time of this submission | Preliminary searches | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Formal screening of search results against eligibility criteria | ☐ | ☑ |
| | | Data extraction | ☐ | ☑ |
| | | Risk of bias (quality) assessment | ☐ | ☑ |
| | | Data analysis | ☐ | ☑ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | | |
| 25. | Review team members | From the National Guideline Centre:<br>Sharon Swain<br>Mark Perry<br>Nicole Downes<br>Sophia Kemmis Betty<br>Elizabeth Pearton | | |
| 26. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. | | |
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. | | |

| ID | Field | Content | |
|---|---|---|---|
| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage]. | |
| 29. | Other registration details | N/A | |
| 30. | Reference/URL for published protocol | | |
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts<br>issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.<br>[Add in any additional agree dissemination plans.] | |
| 32. | Keywords | Diagnosis, Atrial Fibrillation | |
| 33. | Details of existing review of same topic by same authors | N/A | |
| 34. | Current review status | ☐ | Ongoing |
| | | ☒ | Completed but not published |
| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 35.. | Additional information | N/A | |
| 36. | Details of final publication | www.nice.org.uk | |

1

1 **Table 13: 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.<br>• 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).<br>• 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.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• 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 B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003. |
| **Review strategy** | Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>Studies published after 2003 that were included in the previous guideline(s) 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.<br>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.[83]<br><br>**Inclusion and exclusion criteria**<br>• 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.<br>• 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.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>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 in the excluded health economic studies appendix below. |

| | |
|---|---|
| | The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS (most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).<br>• OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis (most applicable).<br>• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be.<br>• Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.<br>• Studies published before 2003 (including any such studies included in the previous guideline(s))will be excluded before being assessed for applicability and methodological limitations.<br>*Quality and relevance of effectiveness data used in the health economic analysis:*<br>• 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. |

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# Appendix B: Literature search strategies

This literature search strategy was used for the following reviews:

- **What is the most clinically and cost-effective risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation?**

- **What is the most accurate risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[83]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

## B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Searches were constructed using the following approaches:

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

**Table 14: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 31 December 2019 | Exclusions<br>Randomised controlled trials<br>Systematic review studies<br>Observational studies<br>Diagnostic tests studies<br>Risk/Prognostic studies |
| Embase (OVID) | 1974 – 31 December 2019 | Exclusions<br>Randomised controlled trials<br>Systematic review studies<br>Observational studies<br>Diagnostic tests studies<br>Risk/Prognostic studies |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2019 Issue 12 of 12<br>CENTRAL to 2019 Issue 12 of 12 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp atrial fibrillation/ |
| 2. | ((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab. |
| 3. | AF.ti,ab. |

| | |
|---|---|
| 4. | 1 or 2 or 3 |
| 5. | letter/ |
| 6. | editorial/ |
| 7. | news/ |
| 8. | exp historical article/ |
| 9. | Anecdotes as Topic/ |
| 10. | comment/ |
| 11. | case report/ |
| 12. | (letter or comment*).ti. |
| 13. | or/5-12 |
| 14. | randomized controlled trial/ or random*.ti,ab. |
| 15. | 13 not 14 |
| 16. | animals/ not humans/ |
| 17. | exp Animals, Laboratory/ |
| 18. | exp Animal Experimentation/ |
| 19. | exp Models, Animal/ |
| 20. | exp Rodentia/ |
| 21. | (rat or rats or mouse or mice).ti. |
| 22. | or/15-21 |
| 23. | 4 not 22 |
| 24. | limit 23 to English language |
| 25. | (stroke or strokes).ti,ab. |
| 26. | ((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab. |
| 27. | (CVA or poststroke or poststrokes).ti,ab. |
| 28. | exp Intracranial Hemorrhages/ |
| 29. | (brain adj2 (attack* or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab. |
| 30. | ((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. |
| 31. | exp Brain infarction/ |
| 32. | *Thromboembolism/ |
| 33. | exp "Intracranial Embolism and Thrombosis"/ |
| 34. | exp Carotid Artery Thrombosis/ |
| 35. | ((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca* or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab. |
| 36. | ((thrombo* or emboli*) adj2 event*).ti,ab. |
| 37. | troponin*.ti,ab. |
| 38. | or/25-37 |
| 39. | 38 not 22 |
| 40. | limit 39 to English language |
| 41. | exp risk/ |
| 42. | (risk adj3 (assess* or scheme* or rating* or 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. |

| | |
|---|---|
| 43. | Decision Support Systems, Clinical/ or Decision Support Techniques/ |
| 44. | ((decision or assess* or screen*) adj3 (tool* or rule* or instrument* or index* or test* or technique* or analy* or system* or model*)).ti,ab. |
| 45. | (logistic* adj model*).mp. |
| 46. | exp Prognosis/ |
| 47. | exp "Predictive Value of Tests"/ |
| 48. | (prognos* or predict*).ti,ab. |
| 49. | or/41-48 |
| 50. | 40 and 49 |
| 51. | chads*.ti,ab. |
| 52. | cha2ds2*.ti,ab. |
| 53. | "cha(2)ds(2)-vasc".ti,ab. |
| 54. | ("Anticoagulation and Risk Factors in Atrial Fibrillation" or ATRIA).ti,ab. |
| 55. | Q stroke.ti,ab. |
| 56. | ABC Stroke.ti,ab. |
| 57. | or/50-56 |
| 58. | 24 and 57 |
| 59. | randomized controlled trial.pt. |
| 60. | controlled clinical trial.pt. |
| 61. | randomi#ed.ab. |
| 62. | placebo.ab. |
| 63. | randomly.ab. |
| 64. | clinical trials as topic.sh. |
| 65. | trial.ti. |
| 66. | or/59-65 |
| 67. | Meta-Analysis/ |
| 68. | Meta-Analysis as Topic/ |
| 69. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 70. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 71. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 72. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 73. | (search* adj4 literature).ab. |
| 74. | (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. |
| 75. | cochrane.jw. |
| 76. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 77. | or/67-76 |
| 78. | exp "sensitivity and specificity"/ |
| 79. | (sensitivity or specificity).ti,ab. |
| 80. | ((pre test or pretest or post test) adj probability).ti,ab. |
| 81. | (predictive value* or PPV or NPV).ti,ab. |
| 82. | likelihood ratio*.ti,ab. |
| 83. | likelihood function/ |

| | |
|---|---|
| 84. | ((area under adj4 curve) or AUC).ti,ab. |
| 85. | (receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab. |
| 86. | (diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. |
| 87. | gold standard.ab. |
| 88. | or/78-87 |
| 89. | Epidemiologic studies/ |
| 90. | Observational study/ |
| 91. | exp Cohort studies/ |
| 92. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 93. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 94. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 95. | Controlled Before-After Studies/ |
| 96. | Historically Controlled Study/ |
| 97. | Interrupted Time Series Analysis/ |
| 98. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 99. | exp case control study/ |
| 100. | case control*.ti,ab. |
| 101. | Cross-sectional studies/ |
| 102. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 103. | or/89-102 |
| 104. | 58 and (66 or 77 or 88 or 103) |

1 **Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp Atrial Fibrillation/ |
| 2. | ((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab. |
| 3. | AF.ti,ab. |
| 4. | 1 or 2 or 3 |
| 5. | letter.pt. or letter/ |
| 6. | note.pt. |
| 7. | editorial.pt. |
| 8. | case report/ or case study/ |
| 9. | (letter or comment*).ti. |
| 10. | or/5-9 |
| 11. | randomized controlled trial/ or random*.ti,ab. |
| 12. | 10 not 11 |
| 13. | animal/ not human/ |
| 14. | nonhuman/ |
| 15. | exp Animal Experiment/ |
| 16. | exp Experimental Animal/ |
| 17. | animal model/ |
| 18. | exp Rodent/ |
| 19. | (rat or rats or mouse or mice).ti. |

| | |
|---|---|
| 20. | or/12-19 |
| 21. | 4 not 20 |
| 22. | limit 21 to English language |
| 23. | (stroke or strokes).ti,ab. |
| 24. | ((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab. |
| 25. | (CVA or poststroke or poststrokes).ti,ab. |
| 26. | *brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/ |
| 27. | (brain adj2 (attack* or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab. |
| 28. | ((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. |
| 29. | *brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/ |
| 30. | *thromboembolism/ |
| 31. | *brain embolism/ |
| 32. | *Carotid Artery Thrombosis/ |
| 33. | ((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca* or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab. |
| 34. | ((thrombo* or emboli*) adj2 event*).ti,ab. |
| 35. | troponin*.ti,ab. |
| 36. | or/23-35 |
| 37. | 36 not 20 |
| 38. | limit 37 to English language |
| 39. | risk/ or risk factor/ or risk assessment/ |
| 40. | (risk adj3 (assess* or scheme* or rating* or 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. |
| 41. | decision support system/ |
| 42. | ((decision or assess* or screen*) adj3 (tool* or rule* or instrument* or index* or test* or technique* or analy* or system* or model*)).ti,ab. |
| 43. | (logistic* adj model*).mp. |
| 44. | prognosis/ |
| 45. | predictive value/ |
| 46. | (prognos* or predict*).ti,ab. |
| 47. | or/39-46 |
| 48. | 38 and 47 |
| 49. | chads*.ti,ab. |
| 50. | cha2ds2*.ti,ab. |
| 51. | "cha(2)ds(2)-vasc".ti,ab. |
| 52. | ("Anticoagulation and Risk Factors in Atrial Fibrillation" or ATRIA).ti,ab. |
| 53. | Q stroke.ti,ab. |
| 54. | ABC Stroke.ti,ab. |
| 55. | or/48-54 |
| 56. | 22 and 55 |

| | |
|---|---|
| 57. | random*.ti,ab. |
| 58. | factorial*.ti,ab. |
| 59. | (crossover* or cross over*).ti,ab. |
| 60. | ((doubl* or singl*) adj blind*).ti,ab. |
| 61. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 62. | crossover procedure/ |
| 63. | single blind procedure/ |
| 64. | randomized controlled trial/ |
| 65. | double blind procedure/ |
| 66. | or/57-65 |
| 67. | systematic review/ |
| 68. | Meta-Analysis/ |
| 69. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 70. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 71. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 72. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 73. | (search* adj4 literature).ab. |
| 74. | (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. |
| 75. | cochrane.jw. |
| 76. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 77. | or/67-76 |
| 78. | Epidemiologic studies/ |
| 79. | Observational study/ |
| 80. | exp Cohort studies/ |
| 81. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 82. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 83. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 84. | Controlled Before-After Studies/ |
| 85. | Historically Controlled Study/ |
| 86. | Interrupted Time Series Analysis/ |
| 87. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 88. | exp case control study/ |
| 89. | case control*.ti,ab. |
| 90. | Cross-sectional studies/ |
| 91. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 92. | or/78-91 |
| 93. | exp "sensitivity and specificity"/ |
| 94. | (sensitivity or specificity).ti,ab. |
| 95. | ((pre test or pretest or post test) adj probability).ti,ab. |
| 96. | (predictive value* or PPV or NPV).ti,ab. |

| | |
|---|---|
| 97. | likelihood ratio*.ti,ab. |
| 98. | ((area under adj4 curve) or AUC).ti,ab. |
| 99. | (receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab. |
| 100. | (diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. |
| 101. | diagnostic accuracy/ |
| 102. | diagnostic test accuracy study/ |
| 103. | gold standard.ab. |
| 104. | or/93-103 |
| 105. | 56 and (66 or 77 or 92 or 104) |

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

| | |
|---|---|
| #1. | MeSH descriptor: [Atrial Fibrillation] explode all trees |
| #2. | ((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab |
| #3. | AF:ti,ab |
| #4. | #1 or #2 or #3 |
| #5. | (stroke or strokes):ti,ab |
| #6. | ((cerebro* or cerebral*) near/2 (accident* or apoplexy)):ti,ab |
| #7. | (CVA or poststroke or poststrokes):ti,ab |
| #8. | MeSH descriptor: [Intracranial Hemorrhages] explode all trees |
| #9. | (brain near/2 (attack* or hemorrhag* or haemorrhag* or bleed* or infarct*)):ti,ab |
| #10. | ((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) near/3 (hemorrhag* or haemorrhag* or bleed*)):ti,ab |
| #11. | MeSH descriptor: [Brain Infarction] explode all trees |
| #12. | MeSH descriptor: [Thromboembolism] this term only |
| #13. | MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees |
| #14. | MeSH descriptor: [Carotid Artery Thrombosis] explode all trees |
| #15. | ((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca* or anterior circulation or carotid or transient or lacunar) near/3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab |
| #16. | ((thrombo* or emboli*) near/2 event*):ti,ab |
| #17. | troponin:ti,ab |
| #18. | (OR #5-#17) |
| #19. | MeSH descriptor: [Risk] explode all trees |
| #20. | (risk near/3 (assess* or scheme* or rating* or 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 |
| #21. | MeSH descriptor: [Decision Support Systems, Clinical] this term only |
| #22. | MeSH descriptor: [Decision Support Techniques] this term only |
| #23. | ((decision or assess* or screen*) near/3 (tool* or rule* or instrument* or index* or test* or technique* or analy* or system* or model*)):ti,ab |
| #24. | (logistic* near/1 model*) |
| #25. | MeSH descriptor: [Prognosis] explode all trees |
| #26. | MeSH descriptor: [Predictive Value of Tests] 3 tree(s) exploded |
| #27. | (prognos* or predict*):ti,ab |

| | |
|---|---|
| #28. | (OR #19-#27) |
| #29. | #18 AND #28 |
| #30. | chads*:ti,ab |
| #31. | cha2ds2*:ti,ab |
| #32. | cha(2)ds(2)-vasc:ti,ab |
| #33. | ("Anticoagulation and Risk Factors in Atrial Fibrillation" or ATRIA):ti,ab |
| #34. | Q stroke:ti,ab |
| #35. | ABC Stroke:ti,ab |
| #36. | (OR #29-#35) |
| #37. | #4 AND #36 |

## B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the Atrial Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run in Medline and Embase.

**Table 15: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 2003– 31 December 2019 | Exclusions<br>Health economics studies |
| Embase | 2003– 31 December 2019 | Exclusions<br>Health economics studies |
| Centre for Research and Dissemination (CRD) | NHSEED - 2003 to March 2015<br>HTA - 2003 –31 December 2019 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp atrial fibrillation/ |
| 2. | ((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab. |
| 3. | AF.ti,ab. |
| 4. | 1 or 2 or 3 |
| 5. | letter/ |
| 6. | editorial/ |
| 7. | news/ |
| 8. | exp historical article/ |
| 9. | Anecdotes as Topic/ |
| 10. | comment/ |
| 11. | case report/ |
| 12. | (letter or comment*).ti. |
| 13. | or/5-12 |
| 14. | randomized controlled trial/ or random*.ti,ab. |
| 15. | 13 not 14 |

| | |
|---|---|
| 16. | animals/ not humans/ |
| 17. | exp Animals, Laboratory/ |
| 18. | exp Animal Experimentation/ |
| 19. | exp Models, Animal/ |
| 20. | exp Rodentia/ |
| 21. | (rat or rats or mouse or mice).ti. |
| 22. | or/15-21 |
| 23. | 4 not 22 |
| 24. | limit 23 to English language |
| 25. | economics/ |
| 26. | value of life/ |
| 27. | exp "costs and cost analysis"/ |
| 28. | exp Economics, Hospital/ |
| 29. | exp Economics, medical/ |
| 30. | Economics, nursing/ |
| 31. | economics, pharmaceutical/ |
| 32. | exp "Fees and Charges"/ |
| 33. | exp budgets/ |
| 34. | budget*.ti,ab. |
| 35. | cost*.ti. |
| 36. | (economic* or pharmaco?economic*).ti. |
| 37. | (price* or pricing*).ti,ab. |
| 38. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 39. | (financ* or fee or fees).ti,ab. |
| 40. | (value adj2 (money or monetary)).ti,ab. |
| 41. | or/25-40 |
| 42. | 24 and 41 |

1 **Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp atrial fibrillation/ |
| 2. | ((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab. |
| 3. | AF.ti,ab. |
| 4. | 1 or 2 or 3 |
| 5. | letter.pt. or letter/ |
| 6. | note.pt. |
| 7. | editorial.pt. |
| 8. | case report/ or case study/ |
| 9. | (letter or comment*).ti. |
| 10. | or/5-9 |
| 11. | randomized controlled trial/ or random*.ti,ab. |
| 12. | 10 not 11 |
| 13. | animal/ not human/ |

| | |
|---|---|
| 14. | nonhuman/ |
| 15. | exp Animal Experiment/ |
| 16. | exp Experimental Animal/ |
| 17. | animal model/ |
| 18. | exp Rodent/ |
| 19. | (rat or rats or mouse or mice).ti. |
| 20. | or/12-19 |
| 21. | 4 not 20 |
| 22. | limit 21 to English language |
| 23. | health economics/ |
| 24. | exp economic evaluation/ |
| 25. | exp health care cost/ |
| 26. | exp fee/ |
| 27. | budget/ |
| 28. | funding/ |
| 29. | budget*.ti,ab. |
| 30. | cost*.ti. |
| 31. | (economic* or pharmaco?economic*).ti. |
| 32. | (price* or pricing*).ti,ab. |
| 33. | (cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 34. | (financ* or fee or fees).ti,ab. |
| 35. | (value adj2 (money or monetary)).ti,ab. |
| 36. | or/23-35 |
| 37. | 22 and 36 |

1 **NHS EED and HTA (CRD) search terms**

| | |
|---|---|
| #1. | MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES |
| #2. | (((atrial or atria or atrium or auricular) adj3 fibrillat*)) |
| #3. | (AF) |
| #4. | (#1 or #2 or #3) |

2

# Appendix C: Clinical article selection

**Figure 1: Flow chart of clinical study selection for the review of the most clinically and cost-effective risk stratification tool for predicting stroke or thromboembolic events in people with atrial fibrillation**

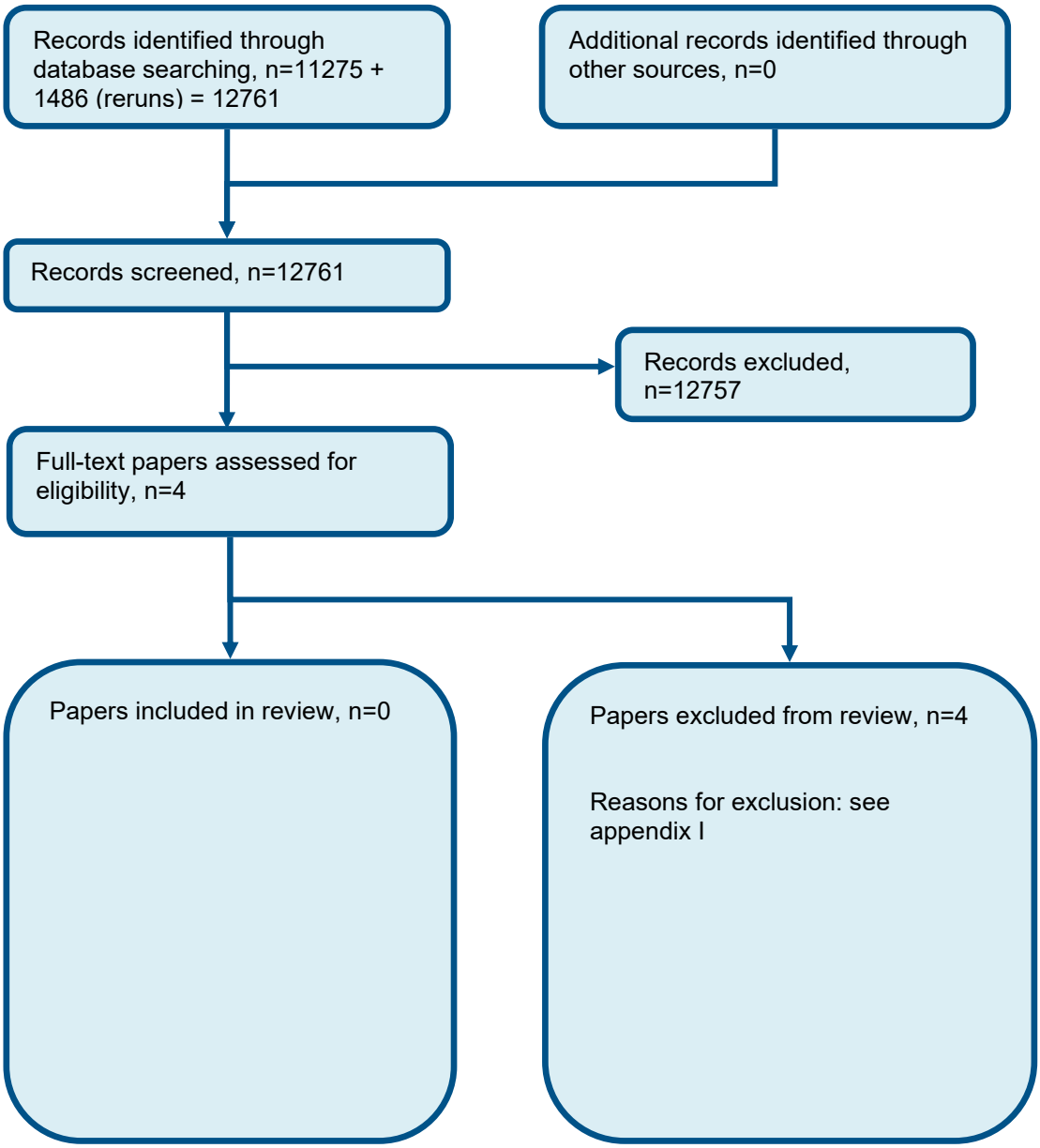
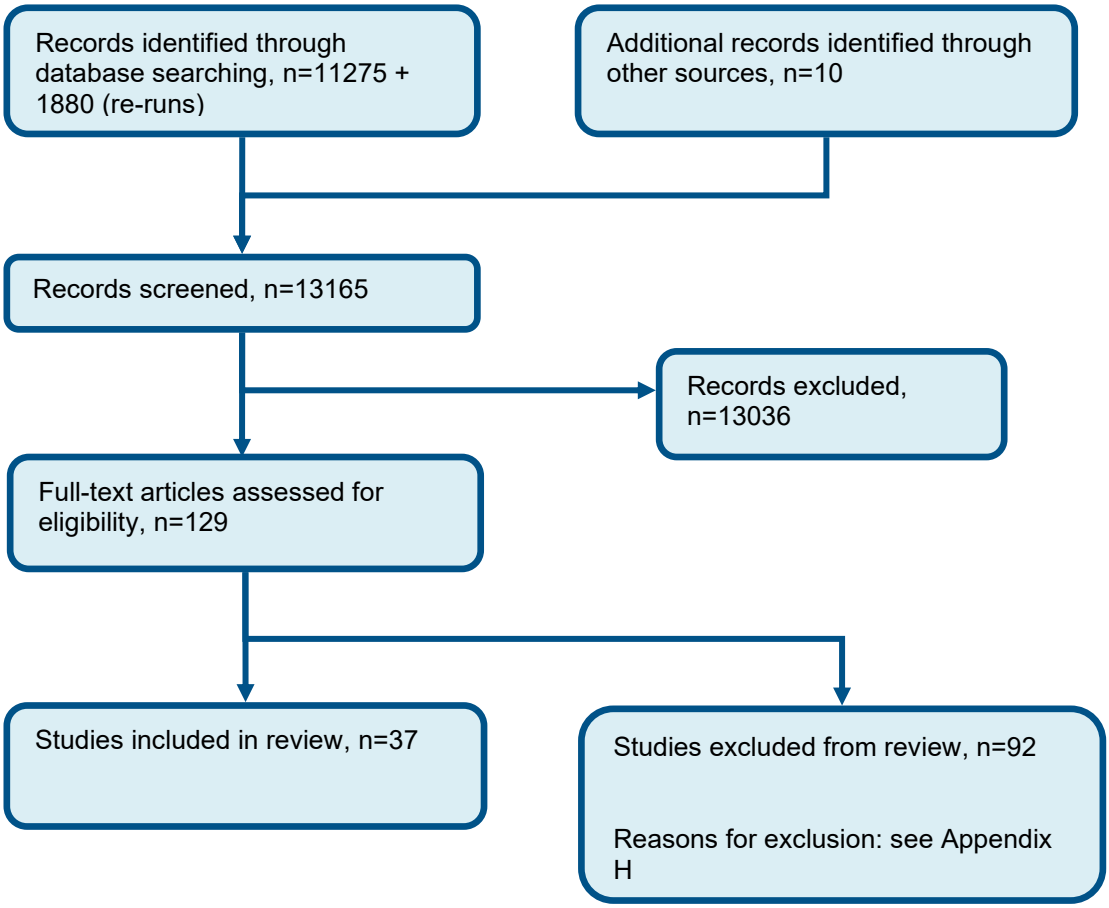


**Figure 2: Flow chart of clinical article selection for the review of 'risk tools for prediction of stroke'.**



# Appendix D: FULL GRADE TABLES (including individual study results)

**Table 16: Clinical evidence profile: Discriminative capacity of stroke prediction tools featured in the studies (see table 3).**

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| CHADS2 | 26 | 572,597 (one study n is unknown) | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | No serious imprecision | 0.65(0.62-0.67)[2]<br>0.69(0.69-0.70)[10]<br>0.66(0.66-0.67)[33]<br>0.82(0.80-0.84)[36]<br>0.58(0.50-0.67)[38]<br>0.61(0.59-0.65)[F] 0.63(0.61-0.66)[M][45]<br>0.74(0.72-0.75)[55]<br>0.64(0.56-0.71)[64]<br>0.67(0.58-0.75)[67]<br>0.57(0.40-0.74)[68]<br>0.66(0.65-0.68)[75]<br>0.70(0.70-0.70)[76]<br>0.81(0.80-0.83)[85]<br>0.63(0.62-0.65)[86]<br>0.66(0.64-0.69)[109]<br>0.51(0.49-0.52)[110]<br>0.68(0.61-0.75)[113]<br>0.64(0.53-0.73)[117]<br>0.68(0.67-0.69)[119]<br>0.66(0.64-0.68)[122] | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0.65(0.60-0.69)[125]<br>0.87(0.81-0.93) [128]<br>0.70(0.68-0.73) [88]<br>**POOLED EFFECT: Random Effects: 0.68(0.65-0.70); $I^2$=98%**<br><br>**Results that could not be pooled due to lack of variance measures:**<br>0.67[27]<br>0.62[123]<br>0.7[35] | |
| Modified CHADS2 (Van Staa, 2010) | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.69(0.67-0.71)[122] | VERY LOW |
| Revised CHADS2 (Friberg 2012) | 2 | 91,574 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.62(0.61-0.62)[33]<br>0.55(0.37-0.73)[68]<br>**POOLED EFFECT: Fixed Effects: 0.62(0.61-0.63); $I^2$=0%** | LOW |
| R2 CHADS2 (Abumaileq 2015, Yoshizaw | 3 | 16846 | Very serious risk of bias[a] | Very serious risk of inconsistency[b] | No serious indirectness | Serious imprecision | 0.65(0.53-0.78)[3]<br>0.85(0.79-0.91)[128]<br>0.70(0.67-0.73) [88]<br>**POOLED EFFECT: Random Effects: 0.74(0.62-0.86); $I^2$=92%** | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| a, 2017, Piccini, 2013) | | | | | | | | |
| R2CHADS2 (71 points) (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.66(0.64-0.67)[75] | LOW |
| CHADS2 KDIGO (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.65(0.64-0.66)[75] | LOW |
| CHADS2 Alb (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.65(0.64-0.67)[75] | LOW |
| CHADS2 eGFR (McAlister, 2017) | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.67(0.65-0.68)[75] | LOW |
| CHADS2 with vWF | 1 | 994 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.69(0.60-0.77)[67] | VERY LOW |
| CHADSVASC 2009 | 26 | 674,678 (in one study n unknown) | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | No serious imprecision | 0.67(0.65-0.69)[2]<br>0.69(0.53-0.85)[3]<br>0.69(0.69-0.70)[10]<br>0.69(0.68-0.69)[20]<br>0.69(0.63-0.76)[30] | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0.67(0.66-0.68)[33]<br>0.72(0.64-0.81)[38]<br>0.62(0.59-0.65)[F] 0.67(0.65-0.69)[M][45]<br>0.71(0.69-0.73)[55]<br>0.66(0.59-0.72)[64]<br>0.64(0.56-0.71)[67]<br>0.58(0.44-0.73)[68]<br>0.66(0.65-0.67)[75]<br>0.62(0.61-0.63)[76]<br>0.89(0.88-0.90[85]<br>0.66(0.65-0.68)[84]<br>0.68(0.66-0.70)[109]<br>0.53(0.51-0.54)[110]<br>0.67(0.61-0.74)[113]<br>0.68(0.67-0.69)[119]<br>0.67(0.65-0.69)[122]<br>0.62(0.57-0.66)[125]<br>0.60(0.51-0.68)[126]<br>0.89(0.85-0.95)[128]<br>0.64(0.58-0.70)[73] ARIC cohort<br>0.68(0.52-0.84) [73] MESA cohort<br>**POOLED EFFECT: Random Effects: 0.68(0.65-0.70); $I^2$=99%**<br><br>**Results that could not be pooled due to lack of variance measures:**<br>0.61[124] | |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| P2-CHADSVASC | 2 | 2929 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.67(0.60-0.75)[73] ARIC cohort<br>0.75(0.60-0.91)[73] MESA cohort<br>**POOLED EFFECT: Fixed effect 0.68 (0.62-0.75) $I^2$=0%** | VERY LOW |
| Age modified CHADSVASC (Chao 2016) | 1 | 124,271 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.71(0.70-0.71)[20] | MODERATE |
| mCHADSVASC (modified in Tomita 2015) | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.60(0.51-0.68)[117] | LOW |
| Modified CHADSVASC (no stroke/TIA)[108] | 1 | 11433 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.65(0.57-0.72)(non-white)[108]<br>0.68(0.64-0.72)(white)[108] | VERY LOW |
| mCHADSVA – (Modified in Tomita 2015) | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.62(0.53-0.71)[117] | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| Q STROKE | 1 | 7689 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.65(0.62-0.67) [Female], 0.71(0.69-0.73)[Male] [45] | LOW |
| ATRIA | 6 | 259,658 (one study unknown n) | Very serious risk of bias[a] | Very serious inconsistency | No serious indirectness | serious imprecision | 0.64(0.49-0.80)[3]<br>0.71(0.70-0.71)[10]<br>0.67(0.66-0.68)[75]<br>0.76(0.755-0.765)[76]<br>0.70(0.67-0.72)[109]<br>0.70(0.69-0.71)[119]<br>**POOLED EFFECT: Random Effects: 0.70 (0.67-0.74); $I^2$=99%** | VERY LOW |
| AFI 1994 | 7 | 182,064 | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | No serious imprecision | 0.58(0.58-0.59)[33]<br>0.68(0.65-0.71)[36]<br>0.60(0.39-0.73)[68]<br>0.60(0.58-0.61)[122]<br>**POOLED EFFECT: Random Effects: 0.62(0.57-0.66); $I^2$=92%**<br><br>**Results that could not be pooled due to lack of variance measures:**<br>0.61[27]<br>0.63[35]<br>0.61[123] | VERY LOW |
| AFI 1998 | 1 | 79,884 | Very serious | No serious inconsistency | No serious indirectness | No serious imprecision | 0.61(0.60-0.62)[122] | LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | risk of bias[a] | | | | | |
| SPAF 1995 | 5 | 90,490 | Very serious risk of bias[a] | Very serious risk of incon-sistency[b] | No serious indirectness | Serious imprecision | 0.74(0.71-0.76)[36]<br>0.63(0.61-0.65)[122]<br>**POOLED EFFECT: Random Effects: 0.68(0.58-0.79); $I^2$=97%**<br><br>**Results that could not be pooled due to lack of variance measures:**<br>0.65[27]<br>0.64[35]<br>0.62[123] | VERY LOW |
| SPAF 1999 | 2 | 91,574 | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Very serious imprecision[c] | 0.63(0.62-0.64)[33]<br>0.51(0.33-0.67)[68]<br>**POOLED EFFECT: Random Effects: 0.60(0.49-0.70); $I^2$=50%** | VERY LOW |
| FRAMINGHAM | 6 | 180331 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.67(0.66-0.68)[33]<br>0.61(0.42-0.79)[68]<br>0.65(0.63-0.68)[122]<br>**POOLED EFFECT: Fixed Effects: 0.67(0.66-0.67); $I^2$=43%**<br><br>**Results that could not be pooled due to lack of variance measures:**<br>0.69[27]<br>0.69[35] | LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0.66[123] | |
| ACCP 2001 | 2 | 82,464 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.58[35]<br>0.62(0.60-0.62)[122]<br>**Range:0.58 to 0.62**<br>**Median: 0.60** | LOW |
| ACCP 2004 | 2 | 85,472 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.6[27]<br>0.61(0.60-0.62)[122]<br>**Range: 0.60 to 0.61**<br>**Median: 0.605** | LOW |
| ACCP 2008 | 2 | 80,968 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.56(0.39-0.73)[68]<br>0.64(0.62-0.65)[122]<br>**POOLED EFFECT: Fixed Effects: 0.64(0.62-0.66); $I^2$=0%** | LOW |
| ACC/AHA/ESC guidelines 2006 | 3 | 171,458 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.62(0.61-0.62)[33]<br>0.55(0.38-0.72)[68]<br>0.64(0.62-0.66)[122]<br>**POOLED EFFECT: Fixed Effects: 0.62(0.61-0.63); $I^2$=47%** | LOW |
| NICE | 3 | 171,458 | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | 0.61(0.60-0.62)[33]<br>0.57(0.42-0.72)[68]<br>0.64(0.62-0.65)[122]<br>**POOLED EFFECT: Random Effects: 0.62(0.59-0.65); $I^2$=72%** | VERY LOW |

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Area Under Curve Individual study effects [point estimate (95% Cis) ] Pooled effect/range /median | Quality |
|---|---|---|---|---|---|---|---|---|
| Hart 1998 | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.62(0.60-0.64)[122] | LOW |
| Van Walraven | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.55(0.54-0.58)[122] | LOW |
| Van Latum | 1 | 79,884 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.57(0.55-0.59)[122] | LOW |
| CHADSVASC with vWF | 1 | 994 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.68(0.59-0.76)[67] | VERY LOW |
| GARFIELD | 1 | 2301 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision | 0.70(0.63-0.77)[30] | VERY LOW |
| SAMe-TT2R2 | 1 | 3483 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | 0.51(0.49-0.53)[69] | LOW |
| Sum of CrCl <60 mL/min and prior stroke/TIA[88] | 1 | 16,360 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.61 (0.58-0.64)[88] | LOW |

1

*Pooling (meta-analysis) was carried out if there were at least two studies per risk tool with confidence intervals. RevMan was used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) Where data were pooled, an $I^2$ of 50-74% was deemed serious inconsistency and an $I^2$ of 75% or above was deemed very serious inconsistency. If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more Cis did not overlap then a rating of serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences. Clinically the studies appeared reasonably homogeneous, with similar rates of hypertension, diabetes and former stroke.*

*c) The judgement of precision was based on the spread of confidence interval across two clinical thresholds: C statistics of 0.5 and 0.7. The threshold of 0.5 marked the boundary between no predictive value better than chance and a predictive value better than chance. The threshold of 0.7 marked the boundary above which the committee might consider recommendations. If the 95% Cis crossed one of these thresholds a rating of serious imprecision was given and if they crossed both of these thresholds a rating of very serious imprecision as given.*

**Table 17: Clinical evidence profile: sensitivity and specificity of stroke prediction tools featured in the studies (see table 3). For pooled data the 95% CIs of individual studies can be found in the Forest plots in the appendices. For individual or non-pooled data the 95% CIs are given below. The pooled sensitivity/specificity values have been calculated using Bayesian methodology and are expressed as medians (95% credible intervals).**

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| CHADS2 at threshold of ≥1 | 6 | 172,747 | **At threshold for risk of ≥1**<br>0.769[46]<br>0.842[10]<br>0.840[2] | **At threshold for risk of ≥1**<br>0.389[46]<br>0.205[10]<br>0.306[2] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0.978[36]<br>0.570[68]<br>0.869[118]<br>**Pooled sensitivity: 0.874(0.676-0.960)** | 0.072[36]<br>0.537[68]<br>0.307[118]<br>**Pooled specificity: 0.228(0.131-0.501)** | **specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADS2 at threshold of ≥2 | 5 | 165,058 | **At threshold for risk of ≥2**<br>0.743[10]<br>0.365[2]<br>0.790[36]<br>0.320[68]<br>0.638[118]<br>**Pooled sensitivity: 0.582(0.308-0.811)** | **At threshold for risk of ≥2**<br>0.409[10]<br>0.787[2]<br>0.344[36]<br>0.814[68]<br>0.634[118]<br>**Pooled specificity: 0.625(0.363-0.835)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADS2 at threshold of ≥3 | 5 | 165,058 | **At threshold for risk of ≥3**<br>0.495[10]<br>0.133[2]<br>0.550[36]<br>0.148[68]<br>0.405[118]<br>**Pooled sensitivity: 0.316(0.129-0.593)** | **At threshold for risk of ≥3**<br>0.707[10]<br>0.935[2]<br>0.649[36]<br>0.932[68]<br>0.844[118]<br>**Pooled specificity: 0.845(0.641-0.944)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | VERY LOW |
| | 1 | 90,490 | | | **Sensitivity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Revised CHADS2 (Friberg 2012) | | | 0.980[33] at standard threshold [no raw data in paper, and no 95% CIs reported] | 0.150[33] at standard threshold [no raw data in paper, and no 95% CIs reported] | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| R2CHADS2 (71 points) (McAlister, 2017) | 1 | 7340 | 0.800[79] no specified threshold | 0.511[79] no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADS2 KDIGO (McAlister, 2017) | 1 | 7340 | 0.726[79] no specified threshold | 0.575[79] no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | 1 | 7340 | | | **Sensitivity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| CHADS2 Alb (McAlister, 2017) | | | 0.821[79] no specified threshold | 0.488[79] no specified threshold | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADS2 eGFR (McAlister, 2017) | 1 | 7340 | 0.693[79] no specified threshold | 0.640[79] no specified threshold | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| CHADSVASC 2009 at threshold of ≥1 | 9 | 440,691 | **At threshold for risk of ≥1**<br>0.966[46]<br>0.987[10]<br>1.000[3]<br>0.967[20]<br>0.890[68]<br>1.000[72]<br>0.927[118]<br>0.964[121] | **At threshold for risk of ≥1**<br>0.164[46]<br>0.086[10]<br>0.034[3]<br>0.057[20]<br>0.160[68]<br>0.090[72]<br>0.174[118]<br>0.162[121] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | VERY LOW |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0.999[129]<br>**Pooled sensitivity: 0.977(0.947-0.992)** | 0.025[129]<br>**Pooled specificity: 0.092(0.051-0.156)** | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADSVASC 2009 at threshold of ≥2 | 9 | 438983 | **At threshold for risk of ≥2**<br>0.957[10]<br>0.952[2]<br>1.000[3]<br>0.868[20]<br>0.695[68]<br>0.960[72]<br>0.840[118]<br>0.895[121]<br>0.982[129]<br>**Pooled sensitivity: 0.923(0.850-0.964)** | **At threshold for risk of ≥2**<br>0.195[10]<br>0.168[2]<br>0.158[3]<br>0.169[20]<br>0.450[68]<br>0.249[72]<br>0.372[118]<br>0.297[121]<br>0.088[129]<br>**Pooled specificity: 0.223(0.144-0.328)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | VERY LOW |
| CHADSVASC 2009 at threshold of ≥3 | 8 | 569,938 | **At threshold for risk of ≥3**<br>0.864[10]<br>0.742[2]<br>0.693[20]<br>0.390[68] | **At threshold for risk of ≥3**<br>0.3395[10]<br>0.476[2]<br>0.323[20]<br>0.710[68] | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0.840[72]<br>0.681[118]<br>0.716[121]<br>0.933[129]<br>**Pooled sensitivity: 0.809(0.631-0.913)** | 0.420[72]<br>0.558[118]<br>0.484[121]<br>0.177[129]<br>**Pooled specificity: 0.431(0.287-0.582)** | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| CHADSVASC 2009 at threshold of ≥4 | 8 | 438,829 | **At threshold for risk of ≥4**<br>0.511[121]<br>0.845[129]<br>0.41[2]<br>0.69[10]<br>0.480[20]<br>0.200[68]<br>0.520[72]<br>0.490[118]<br>**Pooled sensitivity: 0.524(0.347-0.695)** | **At threshold for risk of ≥4**<br>0.671[121]<br>0.318[129]<br>0.770[2]<br>0.530[10]<br>0.500[20]<br>0.870[68]<br>0.630[72]<br>0.740[118]<br>**Pooled specificity: 0.646(0.477-0.781)** | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | VERY LOW |
| Modified CHADSVASC (no stroke/TIA)[113] at threshold for risk of >2 | 1 | 11,433 | **At threshold for risk of ≥2**<br>0.821(0.759-0.872)[113] | **At threshold for risk of >2**<br>0.393(0.384-0.402)[113] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious | NA | No serious indirectness | No serious imprecision | LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | risk of bias[a] | | | | |
| Modified CHADSVASC (no stroke/TIA)[113] at threshold for risk of >3 | 1 | 11,433 | **At threshold for risk of ≥3** 0.631(0.559-0.699)[113] | **At threshold for risk of ≥3** 0.612(0.603-0.621)[113] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | Serious imprecision | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| Modified CHADSVASC (no stroke/TIA)[113] at threshold for risk of >4 | 1 | 11,433 | **At threshold for risk of ≥4** 0.359(0.292-0.431)[113] | **At threshold for risk of ≥4** 0.798(0.791-0.805)[113] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| Q STROKE with optimal cut-off at top 63% | 1 | 7689 | 0.825 (0.798-0.849)[46] with optimal cut-off at top 63% | 0.395(0.383-0.407)[46] with optimal cut-off at top 63% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 90% | 1 | 7689 | 0.992(0.984-0.997)[46] with cut-off at top 90% | 0.112(0.105-0.119)[46] with cut-off at top 90% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 85% | 1 | 7689 | 0.979(0.967-0.987)[46] with cut-off at top 85% | 0.167(0.158-0.176[46] with cut-off at top 85% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| Q STROKE with at top 80% | 1 | 7689 | 0.958(0.943-0.971)[46] with cut-off at top 80% | 0.221(0.211-0.231)[46] with cut-off at top 80% | **Sensitivity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| | 1 | 7689 | | | **Sensitivity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Q STROKE with at top 70% | | | 0.890(0.868-0.909)[46] with cut-off at top 70% | 0.325(0.314-0.336)[46] with cut-off at top 70% | Serious risk of bias[a] | NA | No serious indirectness | Serious imprecision[c] | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | MOD |
| ATRIA at threshold for risk of ≥1 | 2 | 158004 | **At threshold for risk of ≥1** 0.994[63][no raw data] 0.985(0.983-0.987)[10] **Median[d]: 0.985(0.983-0.987)** | **At threshold for risk of ≥1** 0.0820[63][no raw data] 0.091(0.089-0.168)[10] **Median[d]: 0.091(0.089-0.168)[10]** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | Serious imprecision[c] | VERY LOW |
| ATRIA at threshold for risk of ≥2 | 1 | 152149 | **At threshold for risk of ≥2** 0.967(0.964-0.970)[10] | **At threshold for risk of ≥2** 0.166(0.164-0.168)[10] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | 1 | 152149 | | | **Sensitivity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| ATRIA at threshold for risk of ≥3 | | | **At threshold for risk of ≥3** 0.958(0.955-0.962)[10] | **At threshold for risk of ≥3** 0.192(0.189-0.194)[10] | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| ATRIA at threshold for risk of ≥4 | 1 | 152149 | **At threshold for risk of ≥4** 0.936(0.931-0.940)[10] | **At threshold for risk of ≥4** 0.241(0.238-0.243)[10] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| ATRIA at threshold for risk of ≥5 | 1 | 152149 | **At threshold for risk of ≥5** 0.894(0.888-0.899)[10] | **At threshold for risk of ≥5** 0.309(0.307-0.312)[10] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | No serious imprecision | LOW |
| | 3 | 158158 | | | **Sensitivity** | | | | |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| ATRIA at threshold for risk of ≥6 | | | **At threshold for risk of ≥6**<br>0.748[63][no raw data]<br>0.831(0.390-0.395)[10]<br>0.444(0.137-0.788)[3]<br>**Median[d]: 0.444(0.137-0.788)** | **At threshold for risk of ≥6**<br>0.610[63] [no raw data]<br>0.393(0.390-0.395)[10]<br>0.510(0.426-0.594)[3]<br>**Median[d]: 0.510(0.426-0.594)** | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | Serious inconsistency | No serious indirectness | Serious imprecision[c] | VERY LOW |
| ATRIA at threshold for risk of ≥7 | 2 | 152303 | **At threshold for risk of ≥7**<br>0.698(0.689-0.706)[10]<br>0.444(0.137-0.788)[3]<br>**Median[d]: 0.444(0.137-0.788)** | **At threshold for risk of ≥7**<br>0.527(0.524-0.529)[10]<br>0.607(0.522-0.687)[3]<br>**Median[d]: 0.607(0.522-0.687)** | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | VERY LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | LOW |
| AFI 1994 | 1 | 90,490 | 0.990[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.090[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| SPAF 1999 | 1 | 90,490 | 0.890[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.290[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| FRAMINGHAM | 1 | 90,490 | 0.920[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.260[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| ACC/AHA/ESC guidelines 2006 | 1 | 90,490 | 0.980[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.150[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |

| Prediction tool | No of studies | n | Sensitivity | Specificity | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|
| NICE | 1 | 90,490 | 1.000[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | 0.090[33] at standard threshold[no raw data in paper, and no 95% CIs reported] | **Sensitivity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |
| | | | | | **Specificity** | | | | |
| | | | | | Very serious risk of bias[a] | NA | No serious indirectness | NA | LOW |

*Pooling (meta-analysis) was carried out if there were at least three studies per risk tool with confidence intervals. RevMan and WinBugs were used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*

*a) Risk of bias was assessed using the PROBAST checklist. Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) Where data were pooled, inconsistency was assessed by visual inspection of the sensitivity/specificity plots, or data (if 2 studies). The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals. For single studies no evaluation was made and 'not applicable' was recorded.*

*c) Imprecision was assessed based on inspection of the confidence region in the meta-analysis or, where meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60 for sensitivity and 0.5 and 0.1 for specificity), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.*

*d)For unpooled data the median value was given (of data with 95% CIs). If there were an even number of data points in the unpooled data, the data point chosen in the central pair was the one with lower sensitivity, with its paired specificity.*

**Table 18: Clinical evidence profile: D statistics of prediction tools featured in the studies (see table 3)**

| Risk tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | D statistic (95%CI) | Quality |
|---|---|---|---|---|---|---|---|---|
| Q Stroke [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.820(0.660-0.990) [Female][46] | MODERATE |
| Q Stroke [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 1.150(1.000 to 1.300) [Male][46] | LOW |
| CHADS2 [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.640(0.490-0.810) [Female][46] | MODERATE |
| CHADS2 [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.810(0.660 to 0.960) [Male][46] | MODERATE |
| CHADSVASC [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.670(0.510-0.830) [Female][46] | MODERATE |
| CHADSVASC [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 0.970(0.820 to 1.120) [Male][46] | LOW |

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for most risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the Framingham risk tool because the study concerned also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) The judgement of precision was based on the spread of confidence intervals around the clinically important point at 1.1. If the CIs crossed 1.1 then they were graded as seriously imprecise*

**Table 19: Clinical evidence profile: calibration statistics of prediction tools featured in the studies (see table 3)**

| Prediction tool | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | $R^2$ (95%CI) | Hosmer-Lemeshow statistics | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Q Stroke [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.140(0.092-0.187)[Female] [46] | - | MODERATE |
| Q Stroke [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.241(0.193-0.289)[Male][46] | - | MODERATE |
| CHADS2 [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.091(0.049-0.132)[Female] [46] | - | MODERATE |
| CHADS2 [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.135(0.091-0.179) [Male][46] | - | MODERATE |
| CHADSVASC [female] | 1 | 3180 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.096(0.055-0.138)[Female] [46] | - | MODERATE |
| CHADSVASC [male] | 1 | 4509 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision[b] | 0.183(0.137-0.228) [Male][46] | - | MODERATE |
| Framingham | 1 | 705 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | NA | - | 7.6[128] (values <20 indicate good calibration. No CIs or p value provided in study. | LOW |

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for most risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the*

1 *Framingham risk tool because the study concerned also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to*
2 *accurately predict risk.*
3 *b) The judgement of precision was based on the spread of confidence intervals around the clinically important point at 0.5. If the CIs crossed 0.5 then they were graded as*
4 *seriously imprecise*.

1 **Table 19: Clinical evidence profile: NRI of prediction tools featured in the studies (see table 3) with CHADS2 as the comparator**

| Prediction tool comparison | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | [NRI(95% CI)](95%CI) | Quality |
|---|---|---|---|---|---|---|---|---|
| ATRIA versus CHADS2 | 4 | 259,504 | Very serious risk of bias[a] | Very serious inconsistency[b] | No serious indirectness | No serious imprecision | +0.160 (0.140-0.170)[10] (This mainly resulted from up-classification (that is, CHADS2 tended to lead to more false negatives)<br>+0.137 (0.120 to 0.153)[124] (Mainly due to down-classification)<br>+0.240 (0.170 to 0.310)[114]<br>+0.008 (-0.010 to 0.026)[79]<br>**POOLED EFFECT: Random effects NRI +0.130 (+0.050 to +0.220); $I^2$=98%** | VERY LOW |
| R2CHADS2 (71 point) versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.015 (-0.036 to 0.006)[79] | VERY LOW |
| R2CHADS2 versus CHADS2 | 1 | 16,360 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 0.226(0.125 to 0.307)[93] | LOW |
| CHADS2 KDIGO versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | -0.026(-0.049 to -0.002)[79] | LOW |
| CHADS2 Alb versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.018 (-0.026 to 0.028)[79] | VERY LOW |
| CHADS2 eGFR versus CHADS2 | 1 | 58,451 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | +0.006 (-0.017 to 0.030)[79] | VERY LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CHASDS2 with vascular disease versus CHADS2 | 1 | 2002 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | +0.400 (0.000 to +0.800)[88] | MODERATE |

*Pooling (meta-analysis) was carried out if there were at least two studies per risk tool with confidence intervals. RevMan was used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*
*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*
*b) Where data were pooled, an $I^2$ of 50-74% was deemed serious inconsistency and an $I^2$ of 75% or above was deemed very serious inconsistency. If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more Cis did not overlap then a rating of serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences. Clinically the studies appeared reasonably homogeneous, with similar rates of hypertension, diabetes and former stroke.*
*c) The judgement of precision was based on the spread of confidence intervals. If the lower 95% CI passed across 0 then this was graded as seriously imprecise*

**Table 20: Clinical evidence profile: NRI of prediction tools featured in the studies (see table 3) with CHADSVASC (or CHADSVASC derivatives) as the comparator**

| Prediction tool comparison | No of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | [NRI(95% CI)](95%CI) | Quality |
|---|---|---|---|---|---|---|---|---|
| ATRIA versus CHADSVASC | 3 | 210,053 | Very serious risk of bias[a] | Very serious inconsistency[b] | No serious indirectness | No serious imprecision | +0.210(0.200-0.230)[10] (This mainly resulted from down-classification (that is, that CHADSVASC tended to lead to more false positives)<br>+0.233 (0.219 to 0.248)[124](wholly due to down classification)<br>+0.250 (0.210 to 0.300)[114]<br>**POOLED EFFECT: Random effects NRI +0.230 (+0.200 to +0.250); $I^2$=79%** | VERY LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Age-modified CHADSVASC versus CHADSVASC | 1 | 124,271 | serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | +0.039 (0.0216 to 0.0459)[20] | MODERATE |
| CHADS2 versus CHADSVASC | 8 | 210,854 | Very serious risk of bias[a] | Very serious inconsistency[b] | No serious indirectness | Serious imprecision[c] | -0.211 (-0.340 to -0.090) [2]<br>-0.166 (-0.291 to -0.039)[38]<br>+0.005(+0.011 to +0.021)[79]<br>+0.017 (0.000 to +4.200)[57]<br>+0.030 (+0.010 to +0.060)[68]<br>-0.142 (-0.230 to -0.060)[90]<br>+0.237 (0.000 to 0.470)[130]<br>**POOLED EFFECT: Random effects NRI -0.020 (-0.060 to +0.020); $I^2$=84%**<br><br>**Not pooled because of lack of 95% CIs:**<br>+0.070[33] | VERY LOW |
| Revised CHADS2 versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.070[33] | LOW |
| Framingham versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.120[33] | LOW |
| SPAF 1999 versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.120[33] | LOW |
| ACC/AHA/ESC versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.070[33] | LOW |
| NICE versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.000[33] | LOW |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| AFI 1994 versus CHADSVASC | 1 | 90,490 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Not applicable | +0.000[33] | LOW |
| CHADS2 versus mCHADSVASC | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.100(-0.280 to 0.080)[122] | VERY LOW |
| CHADS2 versus mCHADSVA | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | Serious imprecision[c] | -0.030 (-0.210 to 0.160)[122] | VERY LOW |
| mCHADSVASC versus mCHADSVA | 1 | 997 | Very serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | +0.110(0.010 to 0.200)[122] | LOW |
| P2-CHADSVASC versus CHADSVASC | 2 | 2929 | Very serious risk of bias[a] | Serious inconsistency[b] | No serious indirectness | No serious imprecision | +0.250(0.130-0.390)[77 2029] ARIC cohort<br>+0.510(0.180-0.860)[77 2029] MESA cohort<br>**POOLED EFFECT: Random effects NRI +0.330 (+0.100 to +0.570); $I^2$=53%** | VERY LOW |

*Pooling (meta-analysis) was carried out if there were at least two studies per risk tool with confidence intervals. RevMan was used to carry out the analyses. If pooling was not possible for risk tools with >1 data point then the range and median value of the study point estimates were recorded. If there were only one data point then only the result from the study was recorded.*

*a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for some risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status, and most did not report loss to follow up, although follow up and number of events were appropriate. Risk of bias was very serious for the rest of the risk tools because many studies with the aforementioned limitations also had insufficient numbers of events (<100) and/or inappropriately short follow up times (<5 years) to be able to accurately predict risk.*

*b) Where data were pooled, an $I^2$ of 50-74% was deemed serious inconsistency and an $I^2$ of 75% or above was deemed very serious inconsistency. If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more Cis did not overlap then a rating of serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences. Clinically the studies appeared reasonably homogeneous, with similar rates of hypertension, diabetes and former stroke.*

*c) The judgement of precision was based on the spread of confidence intervals. If the lower 95% CI passed across 0 then this was graded as seriously imprecise*

# Appendix E: Forest plots

Note that Forest Plots have not been presented for prediction tools with only a single study

## E.1 C statistics

**Figure 3: C statistic in CHADS2**

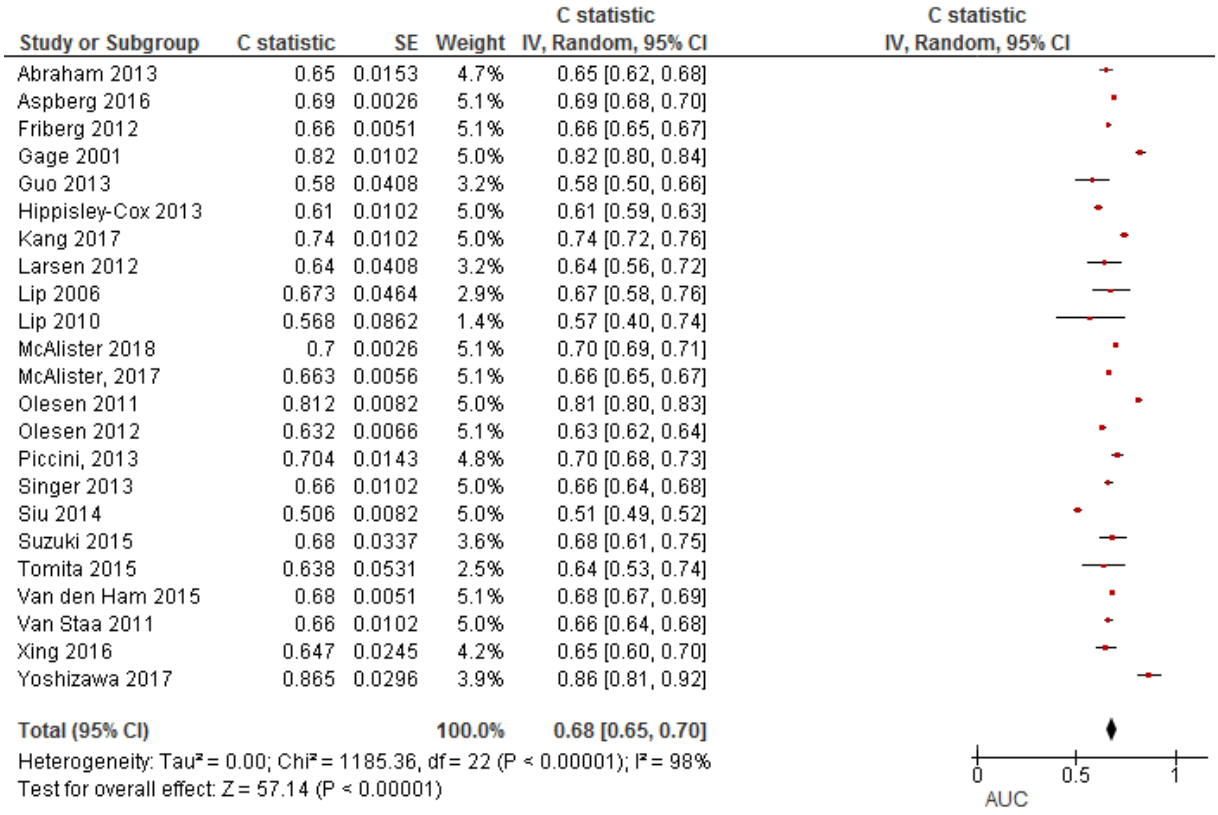



**Figure 4: C statistic in Revised CHADS2**

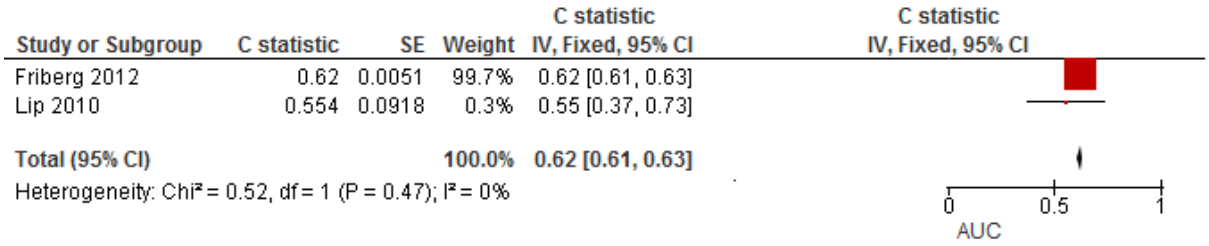



**Figure 5: C statistic in R2CHADS2**

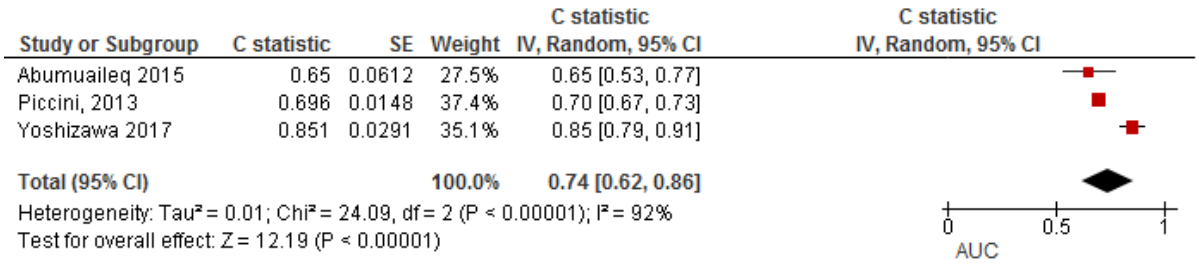



**Figure 6: C statistic in CHADSVASC**

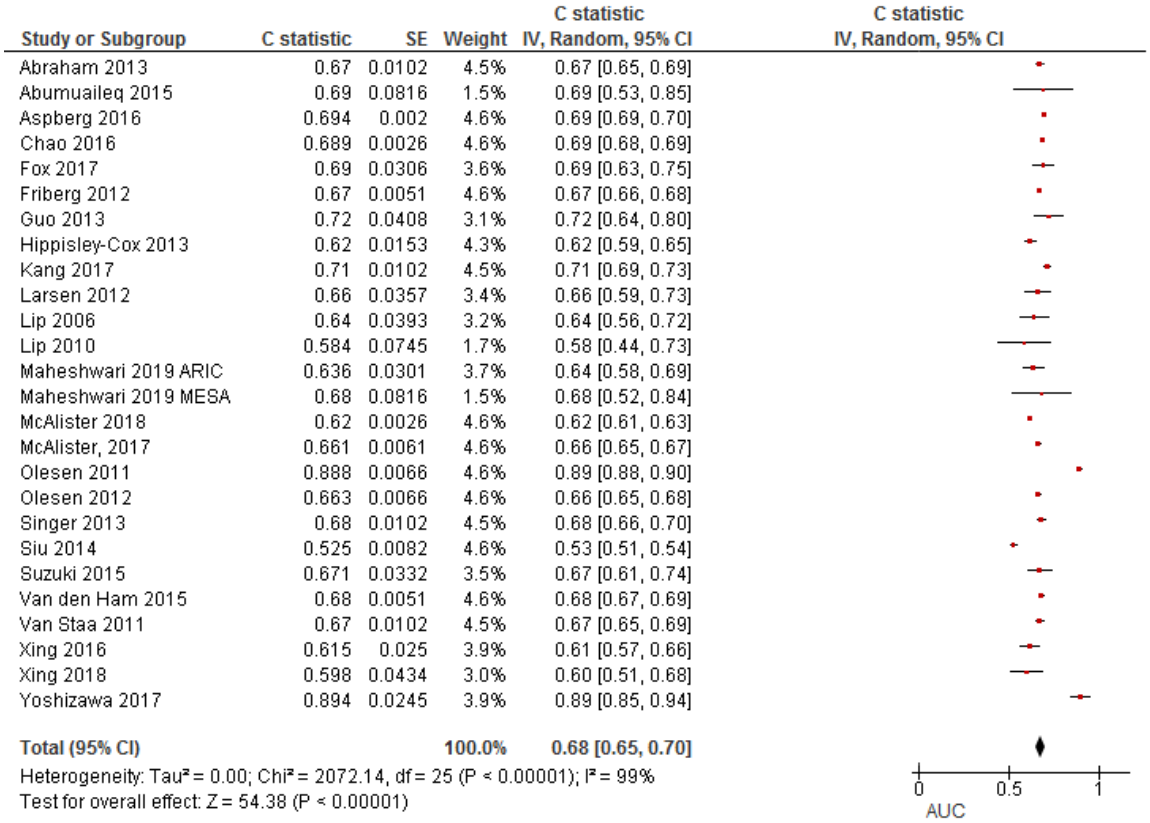



**Figure 7: C statistic in P2-CHADSVASC**

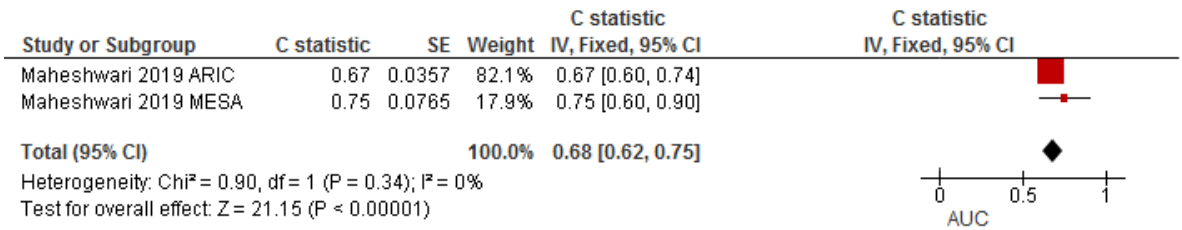



**Figure 8: C statistic in ATRIA**

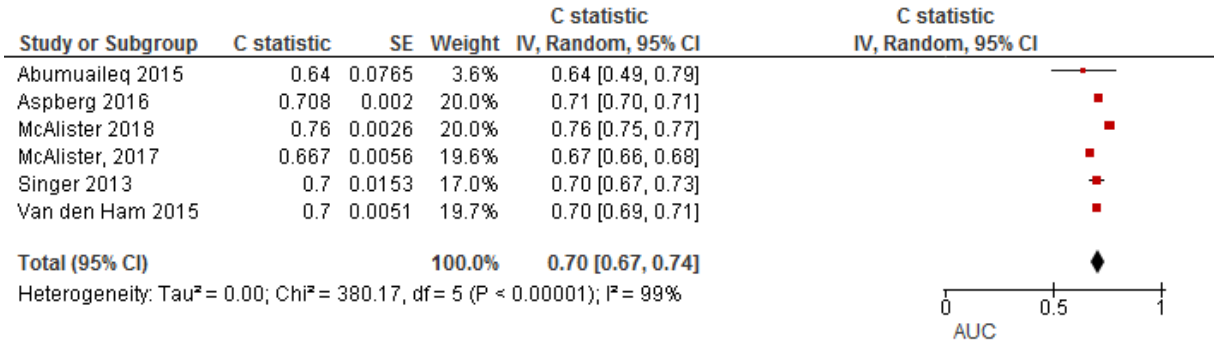



**Figure 9: C statistic in AFI 1994**

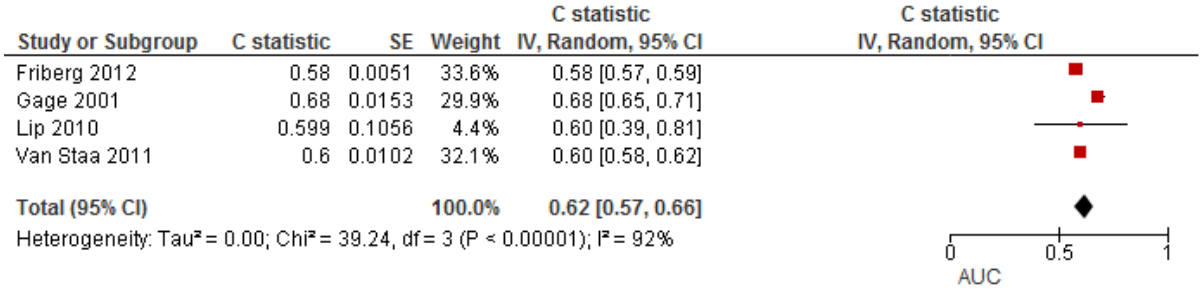



**Figure 10: C statistic in SPAF 1995**

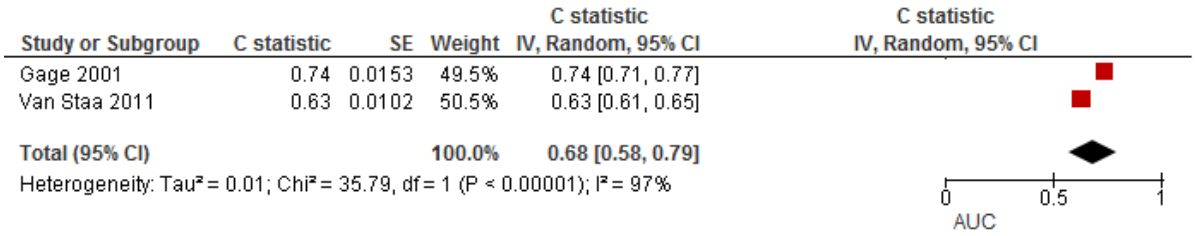



**Figure 11: C statistic in SPAF 1999**

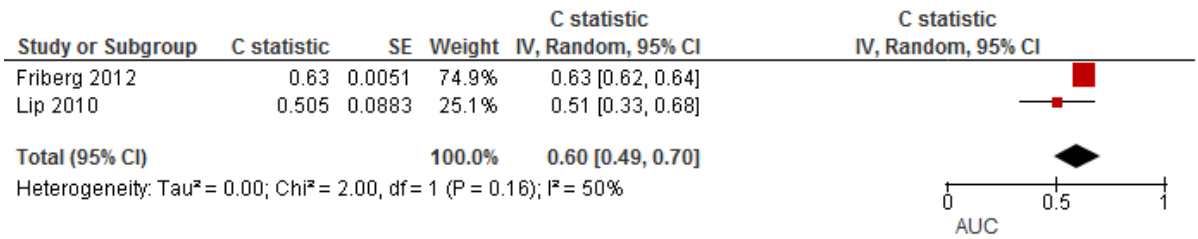



**Figure 12: C statistic in FRAMINGHAM**

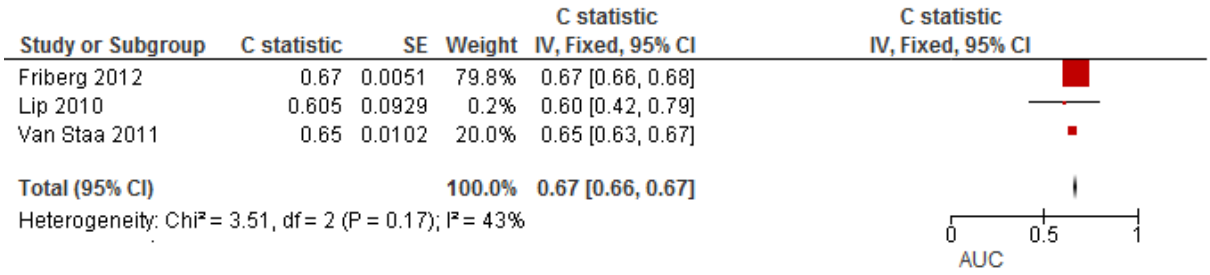



**Figure 13: C statistic in ACCP 2008**

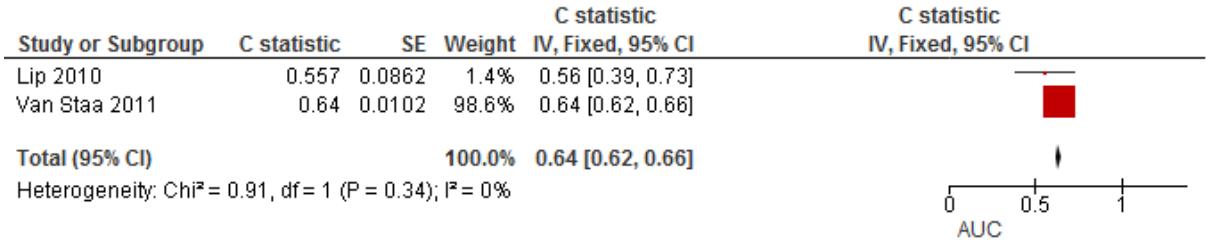



**Figure 14: C statistic in ACH/AHA/ESC**

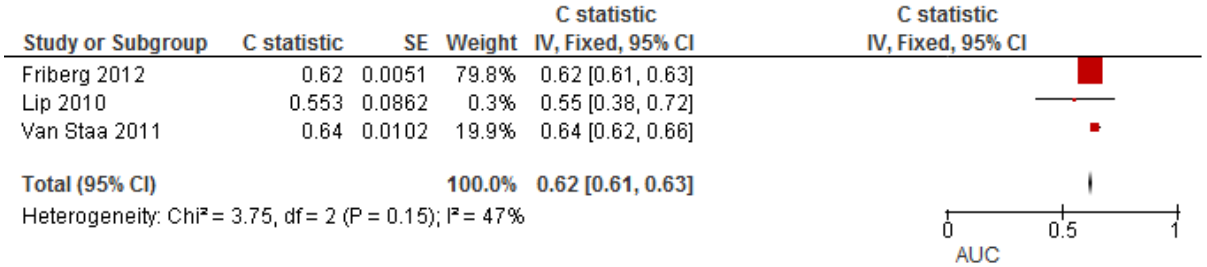
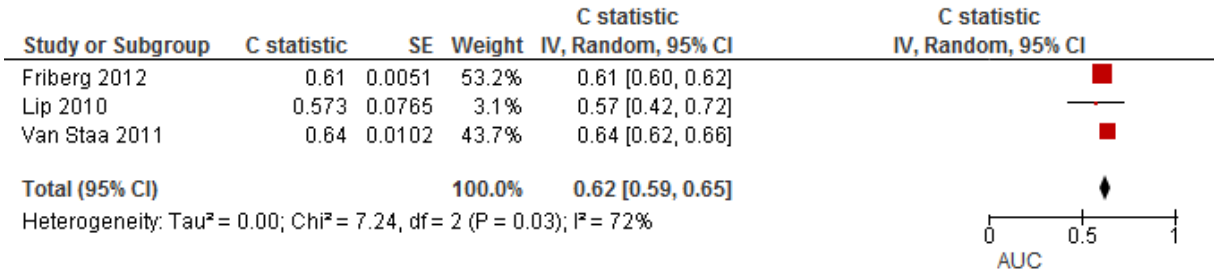


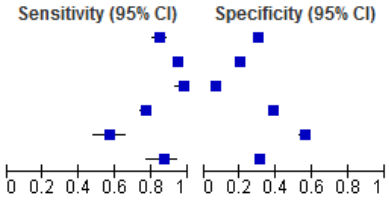

**Figure 15: C statistic in NICE**



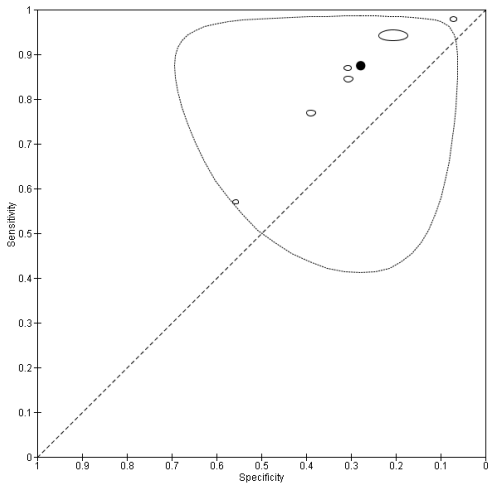

# E.2 Sensitivity/specificity (pooled data only)

**CHADS at threshold of ≥1**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abraham 2013 | 386 | 3835 | 71 | 1689 | 0.84 [0.81, 0.88] | 0.31 [0.29, 0.32] |
| Aspberg 2016 | 10412 | 112082 | 641 | 29018 | 0.94 [0.94, 0.95] | 0.21 [0.20, 0.21] |
| Gage 2001 | 92 | 1521 | 2 | 118 | 0.98 [0.93, 1.00] | 0.07 [0.06, 0.09] |
| HippisleyCox 2013 | 684 | 4153 | 206 | 2646 | 0.77 [0.74, 0.80] | 0.39 [0.38, 0.40] |
| Larsen 2012 | 73 | 653 | 55 | 822 | 0.57 [0.48, 0.66] | 0.56 [0.53, 0.58] |
| Suzuki 2015 | 60 | 2438 | 9 | 1081 | 0.87 [0.77, 0.94] | 0.31 [0.29, 0.32] |



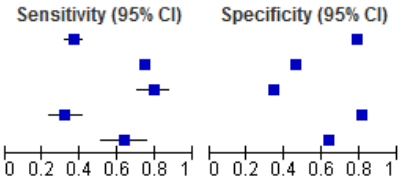

1



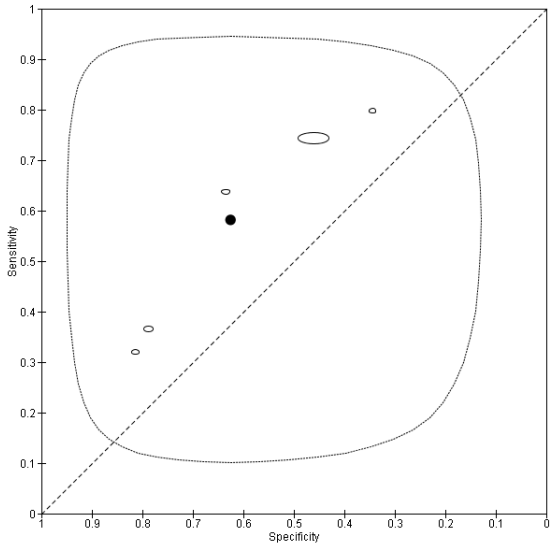

2

3 **CHADS at threshold ≥2**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abraham 2013 | 167 | 1175 | 290 | 4349 | 0.37 [0.32, 0.41] | 0.79 [0.78, 0.80] |
| Aspberg 2016 | 8218 | 76067 | 2835 | 65033 | 0.74 [0.74, 0.75] | 0.46 [0.46, 0.46] |
| Gage 2001 | 75 | 1075 | 19 | 564 | 0.80 [0.70, 0.87] | 0.34 [0.32, 0.37] |
| Larsen 2012 | 41 | 274 | 87 | 1201 | 0.32 [0.24, 0.41] | 0.81 [0.79, 0.83] |
| Suzuki 2015 | 44 | 1285 | 25 | 2234 | 0.64 [0.51, 0.75] | 0.63 [0.62, 0.65] |




4



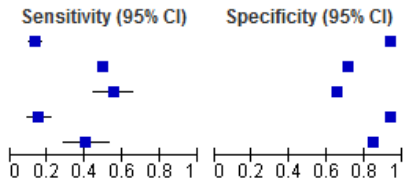

5

6

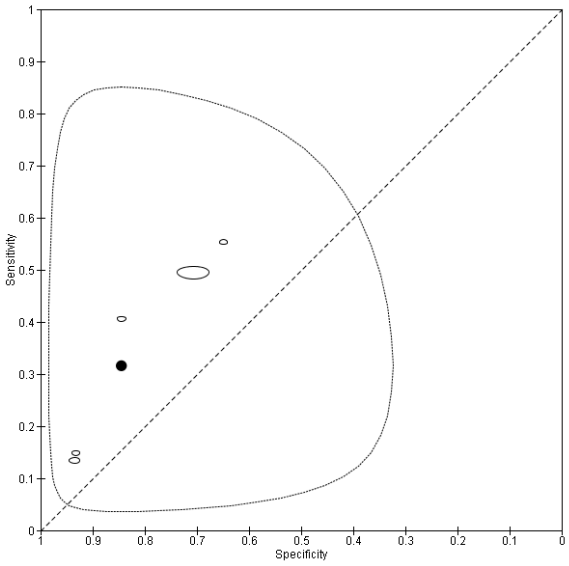
7

8 **CHADS at threshold ≥3**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abraham 2013 | 61 | 359 | 396 | 5165 | 0.13 [0.10, 0.17] | 0.94 [0.93, 0.94] |
| Aspberg 2016 | 5468 | 41292 | 5585 | 99808 | 0.49 [0.49, 0.50] | 0.71 [0.70, 0.71] |
| Gage 2001 | 52 | 575 | 42 | 1064 | 0.55 [0.45, 0.66] | 0.65 [0.63, 0.67] |
| Larsen 2012 | 19 | 100 | 109 | 1375 | 0.15 [0.09, 0.22] | 0.93 [0.92, 0.94] |
| Suzuki 2015 | 28 | 547 | 41 | 2972 | 0.41 [0.29, 0.53] | 0.84 [0.83, 0.86] |




1

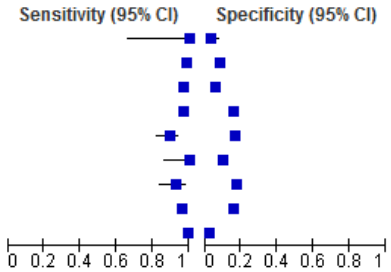



2

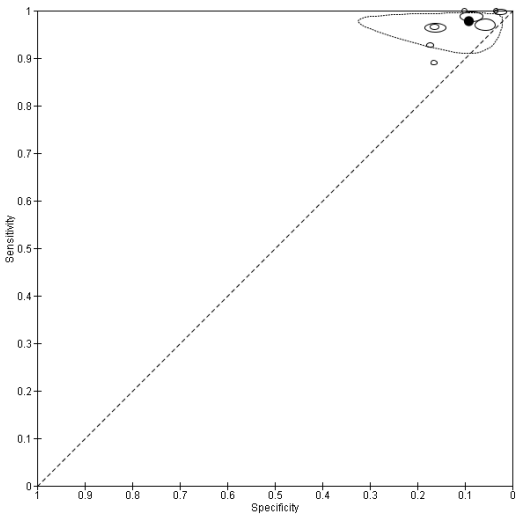
3

4 **CHADSVASC at threshold ≥1**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abumaileq 2015 | 9 | 140 | 0 | 5 | 1.00 [0.66, 1.00] | 0.03 [0.01, 0.08] |
| Aspberg 2016 | 10911 | 128976 | 142 | 12124 | 0.99 [0.98, 0.99] | 0.09 [0.08, 0.09] |
| Chao 2016 | 20373 | 97411 | 635 | 5852 | 0.97 [0.97, 0.97] | 0.06 [0.06, 0.06] |
| HippisleyCox 2013 | 860 | 5684 | 30 | 1115 | 0.97 [0.95, 0.98] | 0.16 [0.16, 0.17] |
| Larsen 2012 | 114 | 1231 | 14 | 243 | 0.89 [0.82, 0.94] | 0.16 [0.15, 0.18] |
| Lip 2010 | 25 | 919 | 0 | 103 | 1.00 [0.86, 1.00] | 0.10 [0.08, 0.12] |
| Suzuki 2015 | 64 | 2907 | 5 | 612 | 0.93 [0.84, 0.98] | 0.17 [0.16, 0.19] |
| Tomasdottir 2019 | 7145 | 94265 | 270 | 18278 | 0.96 [0.96, 0.97] | 0.16 [0.16, 0.16] |
| Wicke 2019 | 1549 | 27959 | 4 | 717 | 1.00 [0.99, 1.00] | 0.03 [0.02, 0.03] |




5

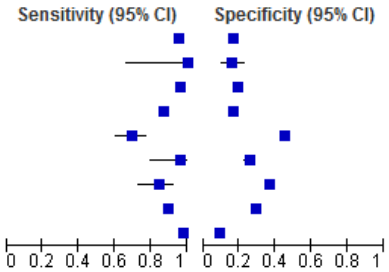


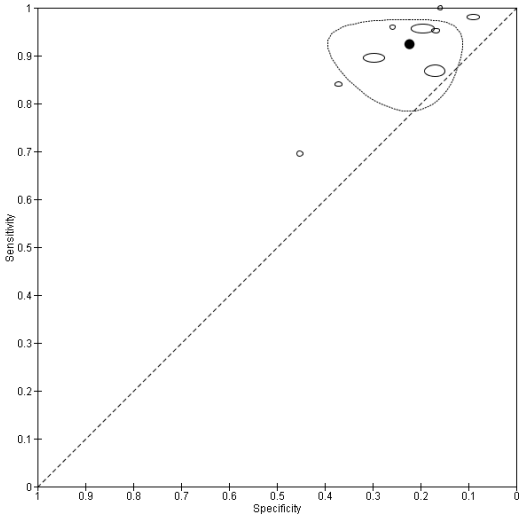

6

7

## CHADSVASC at threshold ≥2

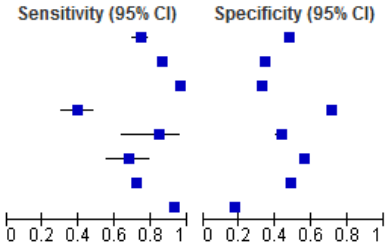
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abraham 2013 | 435 | 4595 | 22 | 929 | 0.95 [0.93, 0.97] | 0.17 [0.16, 0.18] |
| Abumaileq 2015 | 9 | 122 | 0 | 23 | 1.00 [0.66, 1.00] | 0.16 [0.10, 0.23] |
| Aspberg 2016 | 10574 | 113619 | 479 | 27481 | 0.96 [0.95, 0.96] | 0.19 [0.19, 0.20] |
| Chao 2016 | 18235 | 85721 | 2773 | 17542 | 0.87 [0.86, 0.87] | 0.17 [0.17, 0.17] |
| Larsen 2012 | 89 | 807 | 39 | 667 | 0.70 [0.61, 0.77] | 0.45 [0.43, 0.48] |
| Lip 2010 | 24 | 758 | 1 | 264 | 0.96 [0.80, 1.00] | 0.26 [0.23, 0.29] |
| Suzuki 2015 | 58 | 2211 | 11 | 1308 | 0.84 [0.73, 0.92] | 0.37 [0.36, 0.39] |
| Tomasdottir 2019 | 6637 | 79164 | 778 | 33379 | 0.90 [0.89, 0.90] | 0.30 [0.29, 0.30] |
| Wicke 2019 | 1523 | 26104 | 30 | 2572 | 0.98 [0.97, 0.99] | 0.09 [0.09, 0.09] |

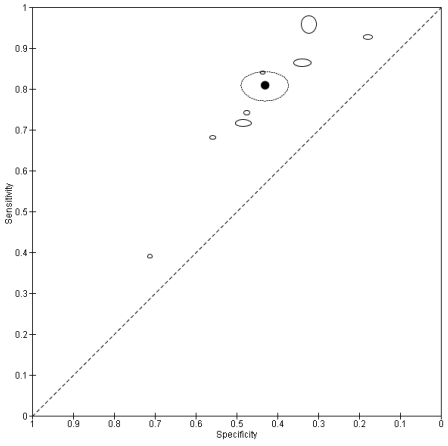



## CHADSVASC at threshold ≥3

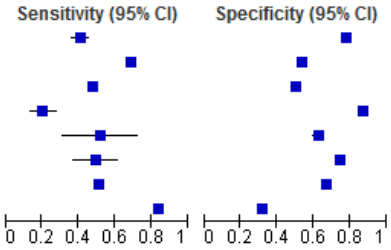
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abraham 2013 | 339 | 2897 | 118 | 2627 | 0.74 [0.70, 0.78] | 0.48 [0.46, 0.49] |
| Aspberg 2016 | 9546 | 93184 | 1507 | 47916 | 0.86 [0.86, 0.87] | 0.34 [0.34, 0.34] |
| Chao 2016 | 145676 | 69851 | 6441 | 33412 | 0.96 [0.96, 0.96] | 0.32 [0.32, 0.33] |
| Larsen 2012 | 50 | 424 | 78 | 1050 | 0.39 [0.31, 0.48] | 0.71 [0.69, 0.74] |
| Lip 2010 | 21 | 577 | 4 | 445 | 0.84 [0.64, 0.95] | 0.44 [0.40, 0.47] |
| Suzuki 2015 | 47 | 1555 | 22 | 1964 | 0.68 [0.56, 0.79] | 0.56 [0.54, 0.57] |
| Tomasdottir 2019 | 5311 | 58123 | 2104 | 54420 | 0.72 [0.71, 0.73] | 0.48 [0.48, 0.49] |
| Wicke 2019 | 1440 | 23551 | 113 | 5125 | 0.93 [0.91, 0.94] | 0.18 [0.17, 0.18] |

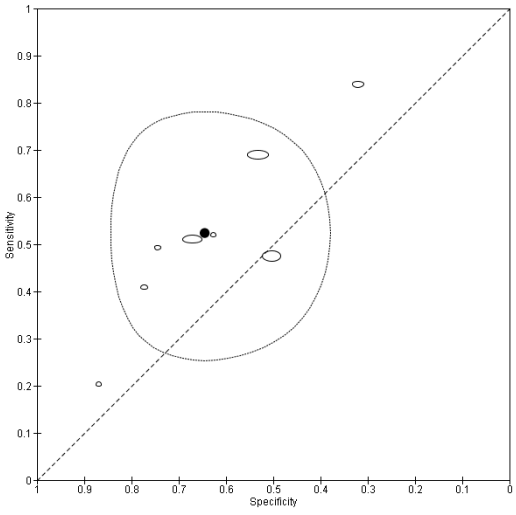



## CHADSVASC at threshold ≥4

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Abraham 2013 | 187 | 1250 | 270 | 4274 | 0.41 [0.36, 0.46] | 0.77 [0.76, 0.78] |
| Aspberg 2016 | 7619 | 65912 | 3434 | 75188 | 0.69 [0.68, 0.70] | 0.53 [0.53, 0.54] |
| Chao 2016 | 9990 | 51314 | 11018 | 51949 | 0.48 [0.47, 0.48] | 0.50 [0.50, 0.51] |
| Larsen 2012 | 26 | 192 | 102 | 1282 | 0.20 [0.14, 0.28] | 0.87 [0.85, 0.89] |
| Lip 2010 | 13 | 382 | 12 | 640 | 0.52 [0.31, 0.72] | 0.63 [0.60, 0.66] |
| Suzuki 2015 | 34 | 899 | 35 | 2620 | 0.49 [0.37, 0.62] | 0.74 [0.73, 0.76] |
| Tomasdottir 2019 | 3787 | 37065 | 3628 | 75478 | 0.51 [0.50, 0.52] | 0.67 [0.67, 0.67] |
| Wicke 2019 | 1303 | 19480 | 250 | 9196 | 0.84 [0.82, 0.86] | 0.32 [0.32, 0.33] |




## E.34 NRI

**Figure 16: ATRIA versus CHADS2**

| Study or Subgroup | NRI | SE | Weight | NRI IV, Random, 95% CI |
|---|---|---|---|---|
| Aspberg 2016 | 0.16 | 0.0102 | 25.9% | 0.16 [0.14, 0.18] |
| McAlister, 2017 | 0.0082 | 0.0093 | 26.0% | 0.01 [-0.01, 0.03] |
| Singer 2013 | 0.24 | 0.0357 | 22.2% | 0.24 [0.17, 0.31] |
| Van den Ham 2015 | 0.137 | 0.0087 | 26.0% | 0.14 [0.12, 0.15] |
| **Total (95% CI)** | | | **100.0%** | **0.13 [0.05, 0.22]** |

Heterogeneity: Tau² = 0.01; Chi² = 165.13, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.12 (P = 0.002)

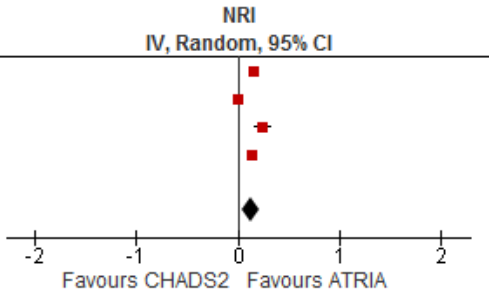



**Figure 17: ATRIA versus CHADSVASC**

| Study or Subgroup | NRI | SE | Weight | NRI IV, Random, 95% CI |
|---|---|---|---|---|
| Aspberg 2016 | 0.21 | 0.0051 | 43.0% | 0.21 [0.20, 0.22] |
| Singer 2013 | 0.25 | 0.0204 | 17.6% | 0.25 [0.21, 0.29] |
| Van den Ham 2015 | 0.233 | 0.0071 | 39.4% | 0.23 [0.22, 0.25] |
| **Total (95% CI)** | | | **100.0%** | **0.23 [0.20, 0.25]** |

Heterogeneity: Tau² = 0.00; Chi² = 9.31, df = 2 (P = 0.010); I² = 79%
Test for overall effect: Z = 20.93 (P < 0.00001)

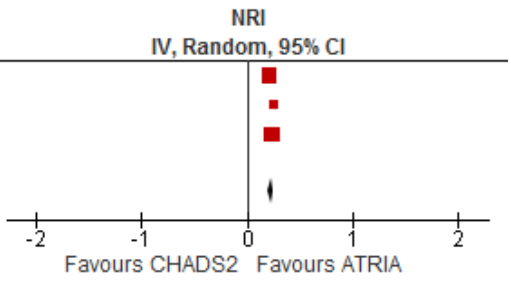


**Figure 18: CHADS2 versus CHADSVASC**

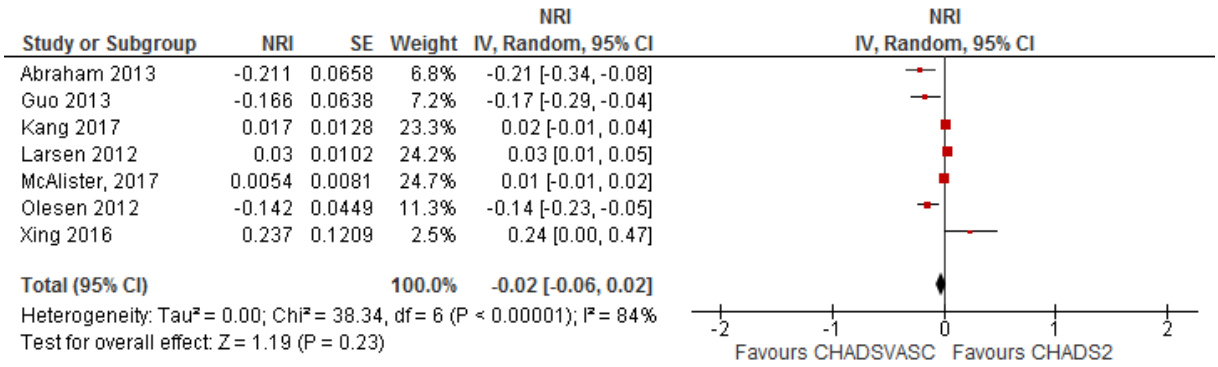
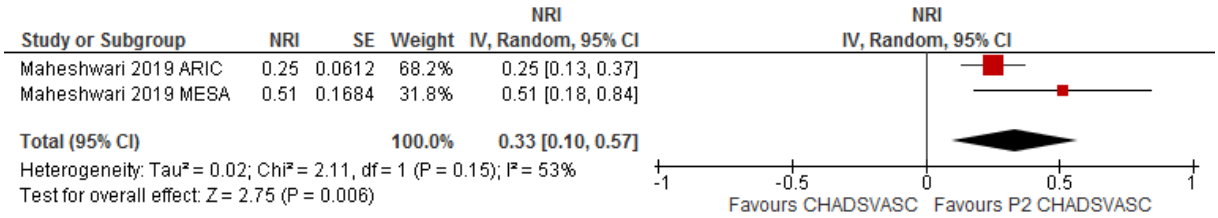



**Figure 19: P2-CHADSVASC versus CHADSVASC**



# Appendix F: Clinical evidence tables

**Table 21. Abraham, 2013[2]**

| Reference | Abraham, 2013 |
|---|---|
| Study type | Retrospective cohort analysis of risk prediction tools |
| Study sample | 161,809 post-menopausal women aged 50-79 years were prospectively enrolled in the Women's Health Initiative (WHI) cohort. Events from 1993 through September 2010 were used for this retrospective analysis. The initial study population consisted of women who reported a history of atrial fibrillation or had an electrocardiogram with documented atrial fibrillation at baseline (n ¼ 7108). From this group, 291 were excluded with valvular heart disease or hyperthyroidism, 85 with missing values for either CHADS2 or CHA2DS2-VASc, and 790 on warfarin or other OACs at WHI randomization or enrolment. There were 1127 excluded, leaving a final sample of 5981, of which 2390 were participants in one of the clinical trials and 3591 were enrolled in the observational study; 5901 women with atrial fibrillation were identified by self-report, 24 by electrocardiogram, and 56 had both. |
| Inclusion criteria | Study participants were members of the Women's Health Initiative (WHI) cohort: a prospective, multiarm clinical trial and observational study that focused on the causes and prevention of cardiovascular disease, cancer, and osteoporosis in women |
| Exclusion criteria | Major exclusion criteria were predicted survival <3 years, alcohol or drug dependency, dementia, severe mental illness, and participation in another clinical trial, valvular heart disease, hyperthyroidism, warfarin or other OACs use. |
| Risk tools | CHADS2 and CHADSVASC |
| Outcome | Intensity of follow-up visits varied based on enrolment arm, ranging from every 6 months (clinical trials) to every 3 years (observational study). When a potential outcome was identified, medical records were obtained and stroke<br>(including self-reports) and transient ischemic attack (only the first event) were centrally adjudicated.<br>Up to 17 year follow up |
| Results | 457 events<br>CHA2DS2-VASc had a higher c statistic than CHADS2:<br>0.67 (95% CI,0.65-0.69) versus<br>0.65 (95% CI, 0.62-0.67), P <.01<br><br>When using CHA2DS2-VASc at 5-year follow-up, the NRI (vs CHADS2) was +0.211, P <.001. |
| Why the group were not anticoagulated | Not a low risk group as 457/5981 with an event at follow up. However the group were somewhat different to a group of warfarin or other OACs users, in terms of a lower risk of: CHF, prior stroke/TIA, and CABG. |

**Table 22**. Abumuaileq, 2015[3]

| Reference | Abumuaileq, 2015 |
|---|---|
| Study type | External validation |
| Study sample | 154 consecutive patients with NVAF, and uncoagulated. All the consultations which were registered in the emergency department of a tertiary hospital between January 2008 and June 2010 enabled identification of all consecutive patients ≥18 years of age with AF documented by electrocardiographic records (n = 1873). After excluding patients with prosthetic valve (n=473), rheumatic heart disease (n = 46) and/or patients with active cancer (n = 61), there were 1293 patients with NVAF. After excluding patients on anticoagulation (n = 1135) and those patients lost to follow up (n = 4) there were 154 consecutive patients with NVAF.<br>Mean age was 74 years, mean SBP was 129, 30% were current smokers, 21% had DM, 6.5% had HF, 15% CHD. 85% CHADSVASC score of 2 points or more |
| Inclusion criteria | Non-valvular AF |
| Exclusion criteria | Patients on anticoagulation, prosthetic valve, rheumatic heart disease, active cancer |
| Risk tools | CHA2DS2-VASc, R2CHADS2 and ATRIA |
| Outcome | 9 TE events<br>The primary endpoint for the present study was the development of TE event during follow-up. A TE complication was defined as the occurrence of ischemic stroke, TIA or peripheral embolism (including fatal TE events). Diagnosis of stroke or transient ischemic attack required an acute neurological deficit lasting for more or less than 24 h, respectively, which could not be explained by other causes and with at least 1 image test (computed tomography or magnetic resonance) compatible with the diagnosis, as well as confirmation from a neurologist. A diagnosis of peripheral embolism was defined as non-central nervous system embolism leading to an abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in absence of another mechanism such as atherosclerosis, instrumentation or trauma.<br>11 month follow up |
| Results | 9 TE events at follow up<br>The C statistics for each tool were as follows:<br>CHADSVASC: 0.69 (0.53 – 0.85)<br>R2CHADS2: 0.65 (0.53 – 0.78)<br>ATRIA: 0.64 (0.49 – 0.80)<br>At the conventional thresholds, CHADSVASC had 100% sensitivity |
| Why the group were not anticoagulated | The non-anticoagulated patients were almost all on antiplatelets, compared to a very small proportion of the anticoagulated patients. They also had a lower prevalence of HF, previous stroke and were more likely to be smokers. |

**Table 23**. Aspberg, 2016[10]

| Reference | Aspberg, 2016 |
|---|---|
| Study type | External validation |
| Study sample | 115,153 participants with AF and no anticoagulant therapy. The SAF Cohort is based on information from two nationwide Swedish health care registers, the National Patient Register and the Prescribed Drug Register. The National Patient Register contains individual information on all hospitalizations and all visits to hospital outpatient clinics in Sweden since 1987. The cases of AF were identified in the National Patient Register. They were defined by ICD code 1409 with or without any of the specifying sub-codes A to F.<br>Prior stroke 13%, Age 70.7% >65 years, 49.3% female, 15.8% DM, 28% HF, 6% Renal failure, 44% hypertension.<br>2005 to 2010 |
| Inclusion criteria | All patients with a diagnosis of AF between 1 July 2005 and 31 December<br>2010 were included. Atrial fibrillation was defined by the ICD-10 code (I489 with or without any of the specifying sub codes A–F). Thus, both AF and atrial flutter were included. |
| Exclusion criteria | The analyses were restricted to patients who did not use anticoagulant therapy during the follow-up period. Patients who were taken care of in the primary care or in other open clinics not affiliated with a hospital during follow-up were not included. |
| Risk tools | ATRIA<br>CHADS<br>CHADSVASC |
| Outcome | Acute ischaemic stroke was the sole outcome event (defined by ICD-10 code I63), excluding TIAs or other kind of thromboembolism sometimes considered in previous studies. The outcome diagnosis, ischaemic stroke, was retrieved from the National Patient Register. A blanking period of 14 days after the index date was used to avoid including events that were registered twice or more due to transfer between hospitals, or reflecting events during the hospital stay possibly occurring prior to the AF diagnosis.<br>The patients were censored at the date when the outcome event occurred, at the date of death, or at end of follow-up (31 December 2010).<br>Follow up 5 years (maximum) |
| Results | 11,053 strokes at follow up (3.25% per year)<br>The total number of patients with a diagnosis of AF during the defined time period was 307 351. After exclusion of patients with mitral stenosis or valvular surgery (13 039) or death within 14 days from the index date (10 343), 283 969 patients remained. Further exclusion of patients given warfarin or other OACs therapy during the follow-up or having a diagnosis of ischaemic stroke within 2 weeks of inclusion, left 152 153 patients for analysis. These patients contributed 340 223 person-years of follow-up, with a mean follow-up time of 2.23 years.<br>The total number of strokes observed during follow-up was 11 053 for an overall ischaemic stroke rate of 3.25%/year.<br>C Index<br>Using the entire point score range: |

| Reference | Aspberg, 2016 |
|---|---|
| | ATRIA: 0.708 (0.704–0.713)<br>CHADS2: 0.690 (0.685–0.695)<br>CHA2DS2-VASc: 0.694 (0.690–0.700).<br>Using the categorical, published cut-points for low, moderate, and high ischaemic stroke risk<br>ATRIA: 0.668 (0.664–0.672)<br>CHADS2: 0.663 (0.658–0.668)<br>CHADSVASC: 0.593 (0.591–0.595).<br><br>However, the C-indices were quite similar when the cut-points in the categorical score were altered to better fit the Swedish cohort's ischaemic stroke rates. ATRIA then had a C-index of 0.633 (0.630–0.635), CHADS2 0.649 (0.646–0.653), and CHA2DS2-VASc 0.634 (0.631–0.637).<br>Using published cut-points for the categorical scores, Net reclassification Improvement (NRI) favoured ATRIA: 0.16 (0.14–0.17) vs. CHADS2 and 0.21 (0.20–0.23) vs. CHA2DS2-VASc.<br>These improvements resulted from<br>predominant up-reclassification of the CHADS2 score (with up-reclassification of events outweighing up-reclassification of non-events)<br>exclusive down-reclassification of the CHA2DS2-VASc score (with down-reclassification of non-events outweighing down-reclassification of events).<br>Net reclassification improvement decreased to near zero when using the optimized cut-points, ATRIA -0.088 -0.022 to 0.0041) vs. CHADS2 and -0.00086 (-0.0094 to 0.0076) vs. CHA2DS2-VASc. |
| Why the group were not anticoagulated | Pre-warfarin or other OACs recommendations. No evidence of low risk or 'special' group. |

**Table 24**. Chao, 2016[20]

| Reference | Chao, 2016 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 124, 271 patients with AF (diagnosed using ICD-9-CM code from the National health Insurance Research database in Taiwan, who had not received warfarin or other OACs or any antiplatelet agents. Age 72, 54% male, 56.8% hypertensive, 23% DM, 38% CHF, 28% previous stroke/TIA. Median CHADSVASC score 3. |

| Reference | Chao, 2016 |
|---|---|
| Inclusion criteria | AF as defined above |
| Exclusion criteria | Warfarin or other OACs or any antiplatelet agents |
| Risk tools | CHADSVASC<br>Age modified CHADSVASC (as original CHADSVASC, but modified by extending the first age criterion from 65-74 to 50-74) |
| Outcome | Ischaemic stroke, with concomitant imaging studies of the brain (CT/MRI)<br>Follow up to 10 years |
| Results | 21,0008 patients had events, for an annual risk of 3.9%<br><br>C indexes for IS<br>CHADSVASC: 0.689 (0.684-0.694)<br>mCHADSVASC: 0.708 (0.703-0.712)<br>DeLong test showed that there was a significant difference (p<0.0001)<br><br>NRI<br>mCHADSVASC v CHADSVASC: +0.039 (0.0216 to 0.0459), p<0.0001 |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 25**. Fang, 2008[27]

| Reference | Fang, 2008 |
|---|---|
| Study type | Retrospective Cohort study |
| Study sample | The ATRIA (AnTicoagulation and Risk Factors In Atrial Fibrillation) study is a cohort of 10,932 adults with diagnosed non-valvular AF and who were not taking Warfarin or other OACs. The study sample relevant to this review were a sub-set of 5,588 patients who were known not to have used anticoagulants from baseline to a fixed follow up of 12 months. Sample data are not given for this sub-group, but the characteristics of the larger sub-group were 46% aged >75, 43% women, 8.3% with prior stroke, 50% with hypertension, 29% with HF and 16% with DM. 81.3% were at moderate or high risk of stroke. |
| Inclusion criteria | Patients with a diagnosis of AF between July 1, 1996, and December 31, 1997, found via automated inpatient, outpatient, and electrocardiographic databases. The cohort was followed up through September 2003, a median follow-up of 6.0 years (interquartile range 3.1 to 6.7 years). |

| Reference | Fang, 2008 |
|---|---|
| Exclusion criteria | Mitral stenosis, documented valvular repair or replacement, transient post-operative AF, or concurrent hyperthyroidism.<br>Warfarin or other OACs exposure among patients was determined from computerized records from pharmacy, laboratory, and ambulatory visits. The analyses were restricted to the 10,932 patients who had periods of time when they appeared not to be taking warfarin or other OACs. |
| Risk tools | AFI 1994, SPAF 1995, CHADS2, Framingham and ACCP 2004 |
| Outcome | Database searched for incident thromboembolic events, either ischemic stroke or other peripheral embolism. The validity of potential events was adjudicated by an outcomes committee of 3 physicians using a formal study protocol. If there was no consensus on the validity of an event, an expert neurologist adjudicated the event. Valid ischemic strokes were defined as neurological deficits of sudden onset that persisted for more than 24 h and were not explained by other etiologies. Valid non-stroke peripheral emboli were defined as emboli identified by radiographic imaging, intraoperative examination, or pathological findings, and without underlying atherosclerotic disease in the affected artery. Outcome events that occurred during hospitalization or as a complication from a diagnostic or interventional procedure were excluded.<br>6 year follow up |
| Results | 685 TEs (643 ISs)<br>C statistics for each tool:<br>AFI 1994 0.61<br>SPAF 1995 0.65<br>CHADS2 0.67<br>Framingham 0.69<br>ACCP 2004 0.60 |
| Why the group were not anticoagulated | Unclear if the non-anticoagulated sample were a special group. No details provided as to why they remained anticoagulated. The 685 events and % at moderate/high risk according to risk tools suggests not a low-risk group. |

**Table 26**. Fox, 2017[30]

| Reference | Fox, 2017 |
|---|---|
| Study type | Retrospective Cohort study |
| Study sample | 2301 patients with AF that were not on OACs. These patients were part of a larger cohort of 10.132 patients enrolled on the UK-based ORBIT-AF registry. Details of the characteristics of these 2301 patients are not reported. |
| Inclusion criteria | People with incident or prevalent AF |
| Exclusion criteria | Not reported |

| Reference | Fox, 2017 |
|---|---|
| Risk tools | GARFIELD AF Risk<br>CHADSVASC |
| Outcome | Stroke/SE defined as the combined end point of IS, SE and TIA. Follow up not reported |
| Results | Untreated cohort (n=2301)<br>C statistics at 1 year (number of events =27)<br>GARFIELD: 0.76(0.68-0.84)<br>CHADSVASC: 0.67(0.61-0.77)<br>C statistics at 3 years (number of events = 51)<br>GARFIELD: 0.70(0.63-0.77)<br>CHADSVASC: 0.69(0.63-0.76) |
| Why the group were not anticoagulated | Unclear. |

**Table 27**. Friberg, 2012[33]

| Reference | Friberg et al. 2012 |
|---|---|
| Study type | Retrospective cohort study. |
| Study sample | 90, 490 patients with AF (defined by ICD-10 code 1489 with or without subscales A-F) identified from the Swedish National Discharge Registry. Demographic data stated to be in supplementary file but not available in that file. |
| Inclusion criteria | All individuals with a diagnosis of AF, between July 2005 and December 2008 who were known to not have used Warfarin or other OACs during the 1.4 year mean follow up. |
| Exclusion criteria | Silent AF and patients with AF taken care of in a primary care setting not affiliated to a hospital; valvular AF, mitral stenosis, valvular surgery. |
| Risk tools | CHADSVASC, CHADS2, SPAF 1999, ACC/AHA/ESC, Framingham, NICE |
| Outcome | First occurrence of Ischaemic stroke (defined by ICD-10 code 163). A blanking period of 14 days was also used, that excluded events occurring in first 14 days. |
| Results | 7334 TE events; 5359 IS events<br>C statistics, sensitivity, specificity and NRI for Ischaemic stroke: |

| Reference | Friberg et al. 2012 | | | | |
|---|---|---|---|---|---|
| | | C statistic (95% Cis) | sensitivity | specificity | NRI |
| | CHADSVASC (continuous) | 0.67(0.66-0.68) | - | - | - |
| | CHADSVASC | 0.56(0.56-0.57) | 1 | 0.06 | Reference |
| | CHADS2 (continuous) | 0.66(0.66-0.67) | - | - | - |
| | Revised CHADS2 | 0.62(0.61-0.62) | 0.98 | 0.15 | 0.07 |
| | CHADS2 | 0.65(0.64-0.65) | 0.98 | 0.15 | 0.07 |
| | Framingham (cont) | 0.67(0.66-0.68) | - | - | - |
| | Framingham | 0.64(0.64-0.65) | 0.92 | 0.26 | 0.12 |
| | SPAF 1999 | 0.63(0.62-0.64) | 0.89 | 0.29 | 0.12 |
| | ACC/AHA/ESC 2006 | 0.62(0.61-0.62) | 0.98 | 0.15 | 0.07 |
| | NICE 2006 | 0.61(0.60-0.62) | 1 | 0.09 | 0.00 |
| | AFI 1994 | 0.58(0.58-0.59) | 0.99 | 0.09 | 0.00 |
| | | | | | |
| Why the group were not anticoagulated | Unclear. Limited demographic information but high number of events suggesting not low risk. | | | | |

**Table 28**. Gage, 2001[36]

| Reference | Gage, 2001 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 1733 patients from the US National Registry of AF cohort. Mean age 81, 58% women, 56% CHF, 56% hypertension, 23% DM, 25% history of cerebral ischaemia. 1204 were not prescribed any antithrombotic therapy and 529 (31%) were prescribed aspirin. CHADS2 score of 2.1. |
| Inclusion criteria | Chronic or recurrent AF – confirmed by ECG or documentation. |

| Reference | Gage, 2001 |
|---|---|
| Exclusion criteria | Acute AF or death during hospitalisation |
| Risk tools | CHADS2 (created in this study by amalgamating the AFI and SPAF schemes), API, SPAF |
| Outcome | Hospitalisation for ischeamic stroke as determined by Medicare claims. ICD-9-CM codes used to identify.<br>1.2 year FU |
| Results | 94 IS events (74 strokes)<br>AFI 1994 0.68 (0.65 to 0.71)<br>SPAF 1995: 0.74 (0.71 to 0.76)<br>CHADS: 0.82 (0.80 to 0.84) |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 29**. Gage, 2004[35]

| Reference | Gage, 2004 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 2580 patients with nonvalvular AF who were on aspirin therapy (doeses of 75 – 325mg/d) but not on warfarin or other OACs therapy [or on an ineffective dose of 1.25mg/d (n=171) or low dose of 2 mg/d (n=290)]. Data taken from 6 prospective RCTS. 37% women, mean age 72, 46% hypertension, 25% HF, 13% DM, 22% prior stroke or TIA, 18% prior MI/angina. 59% moderate or high risk. |
| Inclusion criteria | Nonvalvular AF (not defined) on aspirin therapy |
| Exclusion criteria | Participants included in any derivation cohorts |
| Risk tools | AFI 1994, SPAF, ACCP 2001, CHADS2, Framingham |
| Outcome | Suspected stroke, confirmed by CT in 98% of incident neurological events. Strokes defined as neurological deficits that persisted > 24 hours and not associated with an intracranial haemorrhage.<br>Mean follow up 1.9 years |
| Results | 207 IS events<br>C statistics<br>AFI 1994 0.63 (sd 0.01)<br>SPAF 1995 0.64 (0.01)<br>ACCP 2001 0.58 (0.01)<br>CHADS2 0.70 (0.02) |

| Reference | Gage, 2004 |
|---|---|
| | Framingham 0.69 (0.02)<br>If prior stroke excluded:<br>AFI 0.61 (sd 0.02)<br>SPAF 1995 0.61 (0.02)<br>ACCP 0.58 (0.02)<br>CHADS2 0.63 (0.03)<br>Framingham 0.62 (0.03) |
| Why the group were not anticoagulated | Unclear |

**Table 30**. Guo, 2013[38]

| Reference | Guo, 2013[38] |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 885 patients with pre-existing diagnosis of permanent, persistent or paroxysmal AF at General Hospital in China between 2007 and 2010. Not using Warfarin or other OACs, Mean age 77, 27% female, 75% hypertensive, 39% DM, 23% HF, 63% CAD, 20.9% prior stroke, renal failure 9.6%. 81.2% high risk on CHADSVASC. |
| Inclusion criteria | Development of new onset AF during admission (defined on ECG or Holter recording) and recorded as an ICD-10 code. |
| Exclusion criteria | Warfarin or other OACs |
| Risk tools | CHADS2<br>CHADSVASC |
| Outcome | Major adverse events (stroke/TE). IS defined as focal neurological deficit of sudden onset lasting >24 hours diagnosed clinically by a neurologist. A TE was IS, PE or peripheral embolism.<br>Follow up mean 1.9 years |
| Results | 55 IS, 2 PEs, 12 DVTs and 16 other STEs (Total 85 TE events)<br>C statistic for TEs<br>CHADS2: 0.58 (0.50 to 0.67)<br>CHADSVASC: 0.72 (0.64 to 0.81) |

| Reference | Guo, 2013[38] |
|---|---|
| | NRI<br>CHADSVASC v CHADS: +0.166 (0.039 to 0.291), p=0.009<br><br>IDI<br>+0.011 (0.001 to 0.017) |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 31**. Hippisley-Cox, 2013[46]

| Reference | Hippisley-Cox, 2013 |
|---|---|
| Study type | Internal validation study as this was a joint derivation and validation study, conducted by the same researchers. However the pool of people for the validation study was quite distinct (see below). |
| Study sample | 7689 people on 225 NHS database from GPs who had atrial fibrillation (not defined) at baseline. This was a different random group from the derivation cohort, the derivation cohort being based on 451 completely different NHS practices.<br>Demographic data given for entire dataset, but not for the AF sub-set which the data in this extraction is based on. 71% classed as high risk on CHADS2. |
| Inclusion criteria | People aged 25-84 years at the study entry date, drawn from patients registered with eligible practices between 1 January 1998 and 1 Aug 2012; diagnosis of AF |
| Exclusion criteria | patients with a prior recorded diagnosis of stroke or transient ischaemic attack at baseline because of the difficulty of distinguishing a new stroke from a review of an existing stroke in GP records.<br>patients without a Townsend deprivation score related to a valid postcode.<br>patients who were taking anticoagulants (as defined by chapter 2.8.2 of the British National Formulary) at baseline<br>Did not exclude patients prescribed aspirin at baseline as aspirin is generally not considered to be effective at preventing stroke in patients with atrial fibrillation.<br>Incident users of anticoagulants during follow-up not excluded " in order to ensure the baseline population was representative of patients who might subsequently be prescribed anticoagulants". |
| Risk tools | QStroke (the paper also describes the methodology and results of the derivation of this tool, but not relevant to this review)<br>CHADS<br>CHADSVASC |

| Reference | Hippisley-Cox, 2013 |
|---|---|
| Outcome | First recorded diagnosis of either stroke or transient ischemic attacks, excluding haemorrhagic stroke. The Read codes used for case identification on the GP computer record were those agreed and used in the Quality and Outcomes Framework for General Practice. The ICD-10 codes used for case identification on the Office for National Statistics death certificate were cerebral infarction (I63) and stroke not specified as haemorrhage or infarction (I64).<br>10 year follow up |
| Results | Of the 7689 eligible patients, 890 had a stroke or TIA at follow-up.<br><br>Sensitivity and specificity<br>CHADS2 (score >2): sen 76.9%, spec: 38.9%<br>CHADSVASC (score >2): sen 96.6%, spec: 16.4%<br>Q STROKE (top 63%): sen 82.5%, spec: 39.5%<br>Q STROKE (top 90%): sen 99.2%, spec: 11.2%<br>Q STROKE (top 85%): sen 97.9%, spec: 16.7%<br>Q STROKE (top 80%): sen 95.8%, spec: 22.1%<br>Q STROKE (top 70%): sen 89.0%, spec: 32.5%<br><br>Harrell's C statistic<br>Female<br>Q stroke (95% CIs): 0.65(0.62-0.67)<br>CHADSVASC: 0.62(0.59-0.65)<br>CHADS: 0.61(0.59-0.65)<br>Male<br>Q stroke (95% CIs): 0.71(0.69-0.73)<br>CHADSVASC: 0.67(0.65-0.69)<br>CHADS: 0.63(0.61-0.66)<br><br>R2<br>Female<br>Q stroke (95% CIs): 14(9.2-18.7)<br>CHADSVASC: 9.6(5.5-13.8)<br>CHADS: 9.1(4.9-13.2) |

| Reference | Hippisley-Cox, 2013 |
|---|---|
| | Male<br>Q stroke (95% CIs): 24.1(19.3-28.9)<br>CHADSVASC: 18.3(13.7-22.8)<br>CHADS: 13.5(9.1-17.9)<br><br>D statistic<br>Female<br>Q stroke (95% CIs): 0.82(0.66-0.99)<br>CHADSVASC: 0.67(0.51-0.83)<br>CHADS: 0.64(0.49-0.81)<br><br>Male<br>Q stroke (95% CIs): 1.15(1-1.3)<br>CHADSVASC: 0.97(0.82-1.12)<br>CHADS: 0.81(0.66-0.96)<br><br>NRI<br>Data related to reclassification were given but there were insufficient information on true events and non-events to allow calculation of the NRI (NRI results not provided in the paper) |
| Why the group were not anticoagulated | Unclear but appeared to be not low risk based on the proportion of people with strokes at follow up |

**Table 32**. Kang, 2017[57]

| Reference | Kang, 2017 |
|---|---|
| Study type | Retrospective cohort |
| Study sample | 10,846 patients with newly diagnosed NVAF naïve to oral anticoagulants from the Korean National health Insurance Service national Sample Cohort. Mean age 63.7 years, 47% women, previous stroke 16.7%, CHF 25%, DM 21%, IHD 48%, CHADS more |

| Reference | Kang, 2017 |
|---|---|
| | than or equal to 4: 16%, CHADSVASC more than or equal to 6 10%. 30,138 person-years of follow up (mean follow up time: 2.8years) |
| Inclusion criteria | Non-valvular AF – defined as having AF is 1 or more AF diagnoses made during hospitalisation on 2 or more diagnoses made at outpatient clinics. |
| Exclusion criteria | Rheumatic mitral stenosis, mechanical or bioprosthetic hearts valve, mitral valve repair.<br>Any AF diagnosis during first year following inception of the database to ensure washout period of >1 year<br>Any patients prescribed OACs within 1 month after initial diagnosis of AF (aim was to establish accuracy of tools in people not having OACs at all) |
| Risk tools | CHADSVASC, CHADS2 |
| Outcome | Ischeamic stroke. Stroke was defined according to ICD-10 codes (I63-64) for diagnoses made during hospitalization and according to brain imaging such as computed tomography and magnetic resonance imaging. Patients were censored when they were prescribed oral vitamin K antagonists<br>1.17 years mean follow up |
| Results | 888 events in 29,466 person-years at risk<br><br>The 2 scoring systems were shown to be useful in discriminating the risk of ischemic stroke<br>C statistic, 0.74; 95% confidence intervals [CI]:<br>0.72–0.75 for CHADS2;<br>0.71; 95% CI:0.69-0.73, for CHA2DS2-VASc;<br><br>Harrell's c-index,<br>0.79 for CHADS2 and 0.78 for CHA2DS2-VASc.<br><br>The CHA2DS2-VASc score had a lower NRI than the CHADS2 score<br>−1.7%; 95% CI: −4.2 to 0%; P=0.03. |
| Why the group were not anticoagulated | Unclear – stated as a limitation of study that reasons for prescribing OAC were not identified. |

**Table 33**. Kim, 2017[63]

| Reference | Kim, 2017 |
|---|---|
| Study type | Retrospective cohort |

| Reference | Kim, 2017 |
|---|---|
| Study sample | 5855 OAC naïve AF patients identified from the Korea NHIS sample cohort database from 2002 to 2008. Mean age 64, 48% women, CHADSVASC means core 3.28, 24.5% prior stroke, 13% MI, 32% HF, 76% hypertension, 20% DM. |
| Inclusion criteria | Patients with at least 1 in-patient or 2 out-patient diagnoses of AF. |
| Exclusion criteria | Valvular AF; patients receiving OACs at baseline; <20 years |
| Risk tools | CHADS2, CHADSVASC, ATRIA |
| Outcome | The primary end point was incident ischemic stroke (including ischemic stroke–related death) during the 5 years of follow-up period (from January 2009 to December 2013). Any diagnosis of ischemic stroke with concomitant brain imaging studies, including computed tomography or MRI, was defined as incident ischemic stroke.<br>Mean 4.21 years follow up. |
| Results | 819 strokes<br><br>CHADS sen 85.7, spec 46.8<br>CHADSVASC sen 98.8, spec 16.9<br>ATRIA (0-5) sen 74.8, spec 61<br>ATRIA (0) sen 99.4, spec 8.2<br><br>No C statistics given. |
| Why the group were not anticoagulated | Unclear |

**Table 34**. Larsen, 2012[68]

| Reference | Larsen, 2012 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 1603 non-anticoagulated patients with incident AF (defined by ICD-08 [pre 1994] or ICD-10 codes) from a Danish cohort of 57,053 middle aged people. Age 67, 40% women, mean follow up 5.4 years, CHF 24.4%, 30% hypertension, 10% DM, 6% stroke history. 7% CHADS2 of 5 or above, 6% CHADSVASC score of 5 or above. |
| Inclusion criteria | The study population was defined as incident cases of atrial fibrillation after recruitment who had not emigrated before being diagnosed with atrial fibrillation. |

| Reference | Larsen, 2012 |
|---|---|
| Exclusion criteria | Cases diagnosed simultaneously with stroke, thromboembolism, and transient ischemic attack or patients who died on the same day they were diagnosed with atrial fibrillation were excluded for analysis. Based on the Danish prescription registry, all atrial fibrillation patients having had prescriptions of anticoagulant agents, warfarin or other OACs, or phenprocoumon (ATC code B01AA) within 180 days to the outcome event or end of follow-up were excluded. |
| Risk tools | CHADS2 and CHADSVASC |
| Outcome | Stroke (not defined)<br>5.4 year FU |
| Results | 1.9 strokes per 100 person years<br><br>At mean 5.4 year follow up, C statistics:<br>CHADS2: 0.64 (0.56 – 0.71)<br>CHADSVASC 0.66 (0.59 – 0.72)<br><br>At 1 year follow up, C statistics:<br>CHADS2: 0.68 (0.59 – 0.76)<br>CHADSVASC 0.69 (0.60 – 0.77)<br><br>At 5 year follow up, NRI:<br>CHADSVASC vs CHADS2: -3% (-6% to -1%) |
| Why the group were not anticoagulated | Unclear but cohort were not clearly low risk (56% had CHADSVASC score of 2 or more at baseline). |

**Table 35**. Lip, 2006[71]

| Reference | Lip, 2006 |
|---|---|
| Study type | Retrospective cohort study of data from the RCT SPAF III study |
| Study sample | 994 patients with NVAF, not on adjusted dose warfarin or other OACs therapy (all on aspirin, or aspirin plus low dose 'inefficacious' warfarin or other OACs). Mean age 69.3, 75% male, 53% hypertension, 14% diabetes, 19% recent HF, 13% previous TIA/stroke, 10% previous MI, 6% PVD, 9% LV systolic dysfunction, 8% current smokers. 43 IS events. 73.9% not low risk according to CHADS2. |

| Reference | Lip, 2006 |
|---|---|
| Inclusion criteria | NVAF (not defined in paper) |
| Exclusion criteria | Patients randomised to adjusted-dose warfarin or other OACs |
| Risk tools | CHADS2, Birmingham, CHADS2 with vWF (Plasma von Willebrand Factor Levels) incorporated into the scale, Birmingham with vWF incorporated in to the scale |
| Outcome | Ischaemic Stroke (not defined)<br>1.6 year mean FU |
| Results | 2.32% IS rate<br>C statistics for IS<br>Birmingham: 0.640 (0.563 to 0.713)<br>CHADS2: 0.673 (0.582 to 0.754)<br>Birmingham with vWF: 0.679 (0.591 to 0.756)<br>CHADS2 with vWF: 0.691 (0.600 to 0.772) |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 36**. Lip, 2010[72]

| Reference | Lip, 2010 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 1084 patients without mitral stenosis or previous heart surgery and who did not use VKA or heparin at discharge of qualifying visit and for whom TE outcome was known at 1 year (results from a sub-group analysis of those without ANY use of VKA/heparin during follow up are also given below but exact size and characteristics of this sub-group are not given. However from the %s given the n was around 850). Age 66 years, 41% women, previous stroke 4.2%, TIA 4.3%, DM 17.3%, hypertension 67%, HF 23.5%, antiplatelets 74%, LVEF 53%. 17% classed as high risk and 61.9% as intermediate risk on CHADS2 |
| Inclusion criteria | >18 years, ECG/Holter evidence of AF. |
| Exclusion criteria | Mitral stenosis, previous heart surgery, use of VKAs or Heparin at discharge. |
| Risk tools | AFI 1994, SPAF 1999, CHADS2 (2001), CHADS2 Revised, Framingham, NICE, ACCA/AHA/ESC, ACCP 2008 and Birmingham |
| Outcome | Thromboembolic events: IS (focal neurological event lasting >24 hours diagnosed by neurologist), PE or peripheral embolism |
| Results | C statistic data below are for those known to have been free from warfarin or other OACs throughout follow up (n=850 approx.) |

| Reference | Lip, 2010 |
|---|---|
| | AFI 1994: 0.599(0.392-0.726)<br>SPAF 1999: 0.505(0.332-0.677)<br>CHADS2: 0.568(0.399-0.737)<br>Revised CHADS2: 0.554(0.374-0.734)<br>Framingham: 0.605(0.423-0.787)<br>NICE: 0.573(0.423-0.723)<br>ACC/AHA/ESC: 0.553(0.384-0.722)<br>ACCP 2008: 0.557(0.388-0.725)<br>Birmingham: 0.584(0.438-0.731)<br><br>Data for those that were just VKA free at baseline were qualitatively very similar (not shown here) |
| Why the group were not anticoagulated | Unclear but the cohort are not low risk. |

**Table 37**. Lip, 2014[73]

| Reference | Lip, 2014 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 3,483 patients with AF (n=242 had valvular AF) who were not receiving OACs. Mean age 70, 43% female, 48% HF, 33% CAD, 17% previous MI, 5% previous CABG, 40% hypertensive, 7% previous stroke, 9% renal insufficiency. Mean CHADSVASC score 3.1. |
| Inclusion criteria | Patients given a diagnosis of NVAF or atrial flutter between 2000 and 2010 at Cardiology department in France. |
| Exclusion criteria | OACs |
| Risk tools | SAMe-TT2R2 score |
| Outcome | Stroke/ TEs (not defined)<br>Up to 10 years follow up |
| Results | 273 stroke/TE events<br>Harrel C statistic for stroke/TEs<br>SAMe-TT2R2 score (cont): 0.509 (0.492 to 0.526)<br>SAMe-TT2R2 score (3 cats): 0.514 (0.497 to 0.531) |

| Reference | Lip, 2014 |
|---|---|
| | SAMe-TT2R2 score (2 cats): 0.530 (0.513 to 0.547) |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 38**. Maheshwari, 2019[77]

| Reference | Maheshwari, 2019[77] |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 2229 participants from the ARIC study (Atherosclerosis Risk in Communities) and 700 participants from MESA (Multi-Ethnic Study of Atherosclerosis) with incident AF who were not on anticoagulants within 1 year of AF diagnosis;<br>ARIC cohort: age 73; female 47%; DM 30%; hypertension 75%; previous MI 24%; HF 38%; PAD 9%; past stroke/TIA 15%; CHADSVASC 3.6; black 19%, white 81%;<br>MESA cohort: age 76; female 45%; DM 18%; hypertension 68%; previous MI 6%; HF 8%; PAD 2%; past stroke/TIA 6%; CHADSVASC 3.0; black 20%, white 49%; Chines 13%; Hispanic 17% |
| Inclusion criteria | People enrolled on the ARIC study from 1987-2013 and the MESA study from 2000-2014 |
| Exclusion criteria | From the ARIC study participants with missing ECG data (n=242), missing P-wave indices at baseline (n=45), prevalent AF (n=37), and those who were not white or black from all study sites and non-white from Minneapolis and Washington County (because of the small sample size; n=103) were excluded, resulting in a baseline cohort of 15 365 participants. We then identified 2625 cases of incident AF after the baseline study visit. Because of the potential bias introduced by anticoagulant use when studying stroke risk, participants with anticoagulant use within 1 year of AF diagnosis (n=172) were excluded. We also excluded those without follow-up beyond AF date (n=224), resulting in a final cohort of 2229 participants with incident AF.<br>From the MESA study, participants with prevalent AF (n=66) or missing ECG or P-wave indices at baseline (n=49) were excluded, and we identified 876 cases of incident AF. We then excluded those without follow-up beyond the date of AF diagnosis (n=117), oral anticoagulant use within 1 year of AF diagnosis (n=54), and those with invalid P-wave axis measurements (n=5), resulting in a final cohort of 700 participants with incident AF. |
| Risk tools | CHADSVASC<br>P2-CHADSVASC |
| Outcome | 1 year ischaemic stroke |
| Results | ARIC data<br>Number of ischaemic strokes: 47 at 1 year; 163 at 5 years |

| Reference | Maheshwari, 2019[77] |
|---|---|
| | **C statistic**<br>CHADSVASC 0.60(0.51-0.69) (1 yr)<br>CHADSVASC 0.636 (0.577-0.695) 5 yrs (in online supplement of paper)<br>P2-CHADSVASC 0.67(0.60-0.75) (1 yr)<br>NRI (P2-CHADSVASC v CHASDSVASC at 1 yr)<br>+0.25(0.13-0.86)<br><br>MESA data<br>Number of ischaemic strokes: 31 at 3.3yrs<br>**C statistic**<br>CHADSVASC 0.68(0.52-0.84) (1 yr)<br>P2-CHADSVASC 0.75(0.60-0.91) (1 yr)<br>NRI (P2-CHADSVASC v CHASDSVASC at 1 yr)<br>+0.51(0.18-0.86) |
| Why the group were not anticoagulated | Unclear |

**Table 39**. McAlister, 2017[79]

| Reference | McAlister, 2017 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 58,451 people from Alberta Canada with incident NVAF, and no anticoagulant use. eGFR < 60 24.4%; previous stroke 10.8%; previous bleed 11.2%; age >65 52.6%; female 47%; previous MI: 11.3%; HF: 21.8%; DM: 21.6%; PVD: 3.5%; hypertensive: 64.1% |
| Inclusion criteria | AF defined by ICD ninth revision clinical modification code 427.3 and ICD 10th revision code I48 in any fields of the Alberta health administrative databases; |
| Exclusion criteria | History of aortic or mitral valve disease; valve surgery; end stage renal disease; AF incident in previous 5 years; anticoagulation started in the first 3 months after index NVAF diagnosis. |
| Risk tools | CHADS2, CHADSVASC, R2CHADS2 (71 point), ATRIA, CHADS2KDIGO, CHADS2Alb, CHADS2 eGFR |
| Outcome | Stroke/TE – not defined |

| Reference | McAlister, 2017 | | | | | |
|---|---|---|---|---|---|---|
| | Mean FU: 2.5 years | | | | | |
| Results | 7,340 patients had TES. | | | | | |
| | Tool | Sen | Spec | C statistic | NRI | |
| | CHADS2 | 0.83 | 0.524 | 0.663(0.652-0.657 | Reference | |
| | CHADSVASC | 0.825 | 0.496 | 0.661(0.649-0.672) | -0.0054(-0.0213 to 0.0105) | |
| | R2CHADS2 (71 point) | 0.80 | 0.511 | 0.656(0.644-0.667) | -0.0150(-0.0363 to 0.0063) | |
| | ATRIA | 0.811 | 0.524 | 0.667(0.656-0.679) | +0.0082(-0.0100 to 0.0264) | |
| | CHADS2 KDIGO | 0.726 | 0.575 | 0.650 (0.638-0.663) | -0.0255(-0.0491 to -0.0019) | |
| | CHADS2 Alb | 0.821 | 0.488 | 0.654(0.643-0.666) | -0.0178(-0.0256 to 0.0282) | |
| | CHADS2 eGFR | 0.693 | 0.640 | 0.666(0.653-0.680) | 0.0062(-0.0171 to 0.0295) | |
| Why the group were not anticoagulated | Unclear but clinical characteristics and rate of events (12.6%) suggest cohort was neither low risk nor 'special'. | | | | | |

**Table 40**. McAlister, 2018[80]

| Reference | McAlister, 2018 |
|---|---|
| Study type | Prospective cohorts study |

| Reference | McAlister, 2018 |
|---|---|
| Study sample | This was a sample of people (of an unknown size) with AF (defined as: ICD-9CM 427.3 or ICD-10CA I48) and who were not treated with OACs. No details are given of their characteristics. They were drawn from a larger cohort of 147,952 adult Canadians with AF. |
| Inclusion criteria | AF |
| Exclusion criteria | None reported |
| Risk tools | CHADS2<br>CHADSVASC<br>ATRIA |
| Outcome | First TE: First stroke, TIA or systemic arterial TE |
| Results | C statistics at 1 year for first TE (newly diagnosed [incident])<br>CHADS2: 0.73(0.72-0.73)<br>CHADSVASC: 0.64(0.64-0.64)<br>ATRIA: 0.78(0.78-0.79)<br>C statistics at 1 year for first TE (prevalent patients)<br>CHADS2: 0.70(0.70-0.70)<br>CHADSVASC: 0.62(0.62-0.62)<br>ATRIA: 0.76(0.75-0.76) |
| Why the group were not anticoagulated | Unclear |

**Table 41**. Olesen, 2011[89]

| Reference | Olesen, 2011 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 73,538 people with NVAF who did not receive VKA or heparin. This cohort had almost identical stroke risk scores to others on VKA/heparin (CHADSVASC of 2 or more was 80.5%, comparing to 80.6% for another group with VKA prescription). Age >75 60%, female 51%, DM 9%, previous TE 18%, Vascular disease 18%, antiplatelets 35%. Follow up to 10 years |
| Inclusion criteria | NVAF or atrial flutter (defined by ICD codes ICD-8 [pre 1994] and ICD-10) |

| Reference | Olesen, 2011 |
|---|---|
| Exclusion criteria | VKA or heparin; death or TE in 7 days after baseline; no mitral or aortic valve disease or surgery. Note however that at 10 years 15,344 (20%) had received at least 1 prescription for Warfarin or other OACs, but an unknown sensitivity analysis showed this did not change results. |
| Risk tools | CHADS2 and CHADSVASC |
| Outcome | Admission to hospital, or death, from TE (defined by codes I26,63,64 and 74). |
| Results | Number of events not provided.<br><br>C statistics at 1 year for TE:<br>CHADS2: 0.711<br>CHADSVASC: 0.850<br><br>C statistics at 5 years:<br>CHADS2: 0.796<br>CHADSVASC: 0.880<br><br>C statistics at 10 years:<br>CHADS2: 0.812<br>CHADSVASC: 0.880 |
| Why the group were not anticoagulated | Prior to routine VKA – not a low risk group. |

**Table 42**. Olesen, 2012[88]

| Reference | Olesen, 2012 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 2002 people aged <65 years with NVAF or atrial flutter. Age 54.9, 39% HF, 11% DM, 5% previous stroke, 17% vascular disease, 28.5% female. 38% scored >2 on CHADSVASC. Of these, 924 were not on OACs (results below are only for these), but no demographic data for these provided. |
| Inclusion criteria | NVAF |

| Reference | Olesen, 2012 |
|---|---|
| Exclusion criteria | OACs |
| Risk tools | CHADSVASC<br>CHADS2<br>CHADS2 with vascular disease added |
| Outcome | Stroke and thromboembolism (from documentation)<br>Follow up to 10 years |
| Results | 14 events of TE<br>No accuracy data for CHADSVASC provided.<br>NRI for CHADS2 with vascular disease vs CHADS2<br>+0.4 (0 to 0.8)<br>IDI<br>+0.031, with an area under the ROC improvement of 0.046 (p<0.001) |
| Why the group were not anticoagulated | Unclear if this was not a low risk or special group. |

**Table 43**. Olesen 2012b[90]

| Reference | Olesen 2012b |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 47,576 patients with atrial fibrillation (defined by ICD code I48 from Danish National Patient Registry), not on OACs. Mean age 69.4, CHF 2%, hypertension 17%, DM 2%, previous stroke 0%, vascular disease 12%, female 46.3%, aspirin 26%. 63% CHADSVASC score of 2 or more. All had CHADS2 scores of 0 or 1. |
| Inclusion criteria | NVAF patients |
| Exclusion criteria | OACs |
| Risk tools | CHADSVASC<br>CHADS2 |
| Outcome | Hospitalisation or death from stroke/TE. ICD codes ICD-10: G458, G459, I63,I64,I74)<br>12 year follow up period. |
| Results | At 12 years there were 4599 events |

| Reference | Olesen 2012b |
|---|---|
| | C statistics (12 years)<br>CHADS2: 0.632 (0.619-0.646)<br>CHADSVASC: 0.663 (0.650-0.676)<br>NRI (1 year)<br>CHADSVASC v CHADS2: +0.142, p<0.001<br>IDI (1 year)<br>IDI was 0.003 and the area under the receiver operating curve was improved by 0.042 (p<0.001) |
| Why the group were not anticoagulated | This appears to have been a lower risk group than normal, based on the baseline figures. |

**Table 44**. Piccini, 2013[93]

| Reference | Piccini, 2013 [93] |
|---|---|
| Study type | External validation retrospective cohort study |
| Study sample | Sub-group from the ATRIA cohort that were NOT taking OACS (n=16,360). No information given on characteristics in Piccini, 2013. |
| Inclusion criteria | NVAF patients |
| Exclusion criteria | OACs |
| Risk tools | CHADS2<br>R2CHADS2 score – CHADS2 with creatinine clearance incorporated (2 points for CrCl <60mL/min)<br>Sum of CrCl<60 ml and prior stroke/TIA |
| Outcome | Stroke – a composite of all stroke (both ischemic and haemorrhagic) and systemic embolism. Stroke was defined as a new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that persisted beyond 24 hours and was not attributable to other identifiable causes such as tumour or seizure. Events that involved symptoms that lasted <24 hours were considered TIAs. Brain imaging was sought in each case to distinguish haemorrhagic from ischemic stroke. Non-CNS systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in the absence of another likely mechanism (e.g., atherosclerosis instrumentation, or trauma). In the presence of atherosclerotic peripheral arterial disease, diagnosis of embolism required angiographic demonstration of abrupt arterial occlusion. All suspected primary events were adjudicated by an independent clinical end-point committee that included a stroke neurologist. |
| Results | **[Sub-group NOT taking OACS only]**<br>**C statistics** |

| Reference | Piccini, 2013 [93] |
|---|---|
| | R2CHADS: 0.696 (0.667-0.726)<br>CHADS2: 0.74 (0.676-0.732)<br>Sum of CrCl<60 ml and prior stroke/TIA: 0.625(0.594-0.656)<br><br>**NRI (vs CHADS2)**<br>R2CHADS: 0.226(0.125 to 0.307)<br>**NRI (vs R2CHADS)**<br>Sum of CrCl<60 ml and prior stroke/TIA:-0.024 (-0.077 to + 0.029) |
| Why the group were not anticoagulated | Unclear. |

**Table 45**. Singer, 2013[114]

| Reference | Singer, 2013[114] |
|---|---|
| Study type | Derivation and internal/external validation study of the ATRIA scheme |
| Study sample | Validation cohort: 25, 306 patients with NVAF contributing 26, 263 person-years of follow up off warfarin or other OACs (mean follow up 1 year). TE rate of 1.9% per year (496 stroke or other TE events). Baseline data is only given for the overall (% patient-years) but likely that the validation cohort were similar: female 43%, HF 26%. Hypertension 56%, CAD 29%, PAD 3%, DM 17%, eGFR <60: 35.8% |
| Inclusion criteria | AF confirmed by ECG or physician diagnosis in the medical record (>1 inpatient or >2 outpatient), aged >21. Included also people with mitral stenosis and a history of valve replacement in mitral or aortic positions (1.5% of external validation cohort) |
| Exclusion criteria | Warfarin or other OACs. |
| Risk tools | ATRIA, CHADS2, CHADSVASC |
| Outcome | IS, defined as sudden onset of a neurologic deficit lasting >24 hours and not attributable to other causes. Other TEs: sudden occlusion to an artery to a major organ documented by imaging, surgery or pathology and not due to concomitant atherosclerosis or other causes.<br>Mean FU 1 year |
| Results | 496 TEs<br>C index for stroke/ other TE<br>ATRIA: 0.70 (0.67 to 0.72) (bootstrapped)<br>CHADS2: 0.66 (0.64 to 0.69) |

| Reference | Singer, 2013[114] |
|---|---|
| | CHADSVASC: 0.68 (0.66 to 0.70)<br>NRI<br>Atria v CHADS2: 0.24(0.17-0.31)<br>Atria v CHADSVASC: 0.25(0.21-0.30) |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 46**. Schwartz, 2019[113]

| Reference | Schwartz, 2019[113] |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | Data from 11,443 patients with AF who were NOT on DOACs or VKAs were retrieved from the Northwestern Healthcare system's Enterprise Database Warehouse. The data allowed identification of stroke outcomes, and calculation of prior CHADSVASC scores. Mean age 67.6 for white patients and 63.1 for non-white patients. Mean CHADSVASC was 2.4 in whites and 2.2 in non-whites |
| Inclusion criteria | AF patients with no history of stroke; No use of VKAs or DOACs |
| Exclusion criteria | Patients with missing admission date, unknown race, prescription for dual-antiplatelet agents, and creatine clearance <30 ml/min |
| Risk tools used | CHADSVASC |
| Outcome definition | Incident Stroke using ICD-9 codes and ICD-10 codes |
| Results | **CHADSVASC**<br>**Follow up 971 days post diagnosis; number of stroke events: 205**<br>C statistic ('whites'): 0.681 (0.640-0.721)<br>C statistic ('non-whites'): 0.646(0.572-0.720)<br><br>Accuracy (derived from table 2 in the paper, summating the data in 'whites' and 'non-whites' to produce the overall accuracy figures<br>Threshold of >1, sensitivity 0.8293, spec 0.3931 (TP 170, TN 35, FP 6820, TN 4418).<br>Threshold of >2, sensitivity 0.649, spec 0.6127 (TP 133, TN 72, FP 4352, TN 6885).<br>Threshold of >3, sensitivity 0.3902, spec 0.7987 (TP 80, TN 125, FP 2262, TN 8976). |

| Reference | Schwartz, 2019[113] |
|---|---|
| Why the group were not anticoagulated | **Not reported** |

**Table 47**. Siu, 2014[115]

| Reference | Siu, 2014 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 3881 patients with NVAF (not defined) who did not receive OACs. Mean age 77, 53.5% female, 47.5% hypertensive, 18% DM, 1.7% renal failure on dialysis, 19% HF, 8% CAD, 1.3% PAD, 17% prior stroke/TIA. Mean CHADSVASC 3.3. |
| Inclusion criteria | Non valvular AF |
| Exclusion criteria | Significant valvular heart disease, previous valvular surgery. |
| Risk tools | CHADS2<br>CHADSVASC |
| Outcome | Mean 3.19 year follow up<br>Stroke (not defined) |
| Results | 847 strokes during follow up.<br>C statistics for stroke<br>CHADS2: 0.506 (0.490-0.522)<br>CHADSVASC: 0.525 (0.509-0.541)<br>CHADSVASC sensitivity of 0.98 at cut-off of 1. |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 48**. Suzuki, 2015[118]

| Reference | Suzuki, 2015 |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 3588 patients with AF without anticoagulation. Taken from 3 Japanese databases. Age 68.1, 34% female, 50% hypertension, 15% DM, 8.5% previous stroke or TIA, 15% HF, 11% CAD, 42% antiplatelet use. No data on CHADSVASC scores at baseline |

| Reference | Suzuki, 2015 |
|---|---|
| Inclusion criteria | AF patients (confirmed by 12 lead ECG or Holter monitoring) on one of 3 Japanese patient registries. |
| Exclusion criteria | Anticoagulation at time of registration. |
| Risk tools | CHADS2 and CHADSVASC |
| Outcome | Ischeamic stroke (not defined)<br>Average 1.4 years follow up |
| Results | 69 strokes in follow-up period (in 5.188 person-years)<br>CHADS2: 0.680 (0.614 – 0.746)<br>CHADSVASC: 0.671 (0.606 – 0.736) |
| Why the group were not anticoagulated | Unclear but data on baseline CHADSVASC score not given. However incidence rate of stroke was 1.3%, about half the expected value, suggesting a lower than expected level of risk. |

**Table 49**. Tomasdottir, 2019[121]

| Reference | Tomita, 2015[121] | | | |
|---|---|---|---|---|
| Study type | Retrospective cohort study | | | |
| Study sample | 231 077 (48.1% women) non-selected patients with AF not receiving oral anticoagulation from 2006 to 2014. Data from cross-linked national Swedish registers. Age 75 (men), 82 (women); HF 28.5%; hypertension 48.4%; DM 17.2%; Stroke/TIA/SE 18.7%; Vascular disease 24.1% | | | |
| Inclusion criteria | All patients with an AF diagnosis registered between 2 December 2005 and 31 December 2014 | | | |
| Exclusion criteria | Using OACs within 6 months of start of study (if during follow up were censored at that point); < 18 yrs; mitral stenosis or prosthetic heart valve | | | |
| Risk tools | CHADSVASC | | | |
| Outcome | Ischaemic stroke at mean follow up of 2.5 years | | | |
| Results | **Sensitivity and specificity of CHADSVASC at different thresholds (calculated from data in figure 3 in paper)** | | | |
| | Women | | | |
| | **threshold** | **sensitivity** | **specificity** | |
| | ≥1 | 1 | 0 | |
| | ≥2 | 0.984296 | 0.083649 | |

| | | | | |
|---|---|---|---|---|
| **Reference** | **Tomita, 2015[121]** | | | |
| | ≥3 | 0.946173 | 0.177238 | |
| | ≥4 | 0.785679 | 0.361596 | |
| | ≥5 | 0.546864 | 0.592322 | |
| | ≥6 | 0.328691 | 0.773967 | |
| | ≥7 | 0.142617 | 0.903489 | |
| | ≥8 | 0.039802 | 0.969533 | |
| | ≥9 | 0.007309 | 0.994277 | |
| | | | | |
| | **Men** | | | |
| | **threshold** | **sensitivity** | **specificity** | |
| | ≥1 | 0.963587 | 0.162409 | |
| | ≥2 | 0.895078 | 0.296589 | |
| | ≥3 | 0.716251 | 0.483549 | |
| | ≥4 | 0.510722 | 0.670659 | |
| | ≥5 | 0.306001 | 0.820655 | |
| | ≥6 | 0.141065 | 0.921506 | |
| | ≥7 | 0.04356 | 0.973948 | |
| | ≥8 | 0.007687 | 0.994429 | |
| | | | | |
| | No other predictive data reported | | | |
| Why the group were not anticoagulated | Unclear | | | |

**Table 50**. Tomita, 2015[122]

| Reference | Tomita, 2015 [122] |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 294 women and 703 men with NVAF and no warfarin or other OACs treatment. Mean mCHADSVASC scores of 1.9 (male) and 3.3 (female). , Mean age 687% history of stroke/TIA, 58% antiplatelet use, 29% paroxysmal AF. 2 year follow up. 5 lost to FU |
| Inclusion criteria | AF (not defined) |
| Exclusion criteria | OACs |
| Risk tools | mCHADSVASC excluding female sex from the scheme = mCHADSVA<br>mCHADSVASC<br>CHADS2<br>Note: the m refers to the fact that these did not include PAD. |
| Outcome | TE events – not defined |
| Results | 30 IS events<br>C statistic<br>CHADS2: 0.638 (0.534-0.730)<br>mCHADSVASC: 0.595 (0.504 – 0.680)<br>mCHADSVA: 0.624 (0.531-0.709)<br>NRI<br>CHADS2 versus mCHADSVASC<br>-0.1(-0.28 to 0.08)<br>CHADS2 versus mCHADSVA<br>-0.03 (-0.21 to 0.16)<br>mCHADSVASC versus mCHADSVA<br>+0.11(0.001 to 0.20) |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

**Table 51**. Van den Ham, 2015[124]

| Reference | Van den Ham, 2015[124] |
|---|---|
| Study type | Retrospective cohort study |

| Reference | Van den Ham, 2015[124] |
|---|---|
| Study sample | 60, 594 patients with NVAF untreated with warfarin or other OACs. Mean age 74.4 years, female 48.7%, 50% past or present smokers; 12% DM, 17.5% CHF, 54.6% hypertension, 15% previous stroke/TIA, 31% vascular disease, 28% renal dysfunction (eGFR <60 ml/min/1.73m2). mean follow up time was 2.1 years |
| Inclusion criteria | People with a first AF diagnosis (not defined) aged 18 years or older |
| Exclusion criteria | Rheumatic mitral stenosis, prosthetic heart valve; use of anticoagulants |
| Risk tools | ATRIA, CHADSVASC and CHADS2 |
| Outcome | Ischeamic stroke (defined by codes in CPRD, HES or both)<br>Mean 2.1 year follow up |
| Results | 3751 IS events in follow up period of 125,296 person-years<br>The C statistics for the continuous risk scores were<br>0.70 (95% CI:0.69to0.71) for the ATRIA risk score,<br>0.68 (95% CI: 0.67 to 0.69) for the CHADS2,and<br>0.68 (95% CI: 0.67 to 0.69) for the CHA2DS2-VASc risk score.<br>The categorical risk scores, using the published low/moderate/high risk cut-offs resulted in C statistics of<br>0.66 (95% CI: 0.66 to 0.67) for the ATRIA,<br>0.65 (95% CI: 0.64 to 0.66) for the CHADS2, and<br>0.59 (95% CI: 0.59 to 0.60) for the CHA2DS2-VASc risk score.<br><br>The NRI was 0.137 (95% CI: 0.120 to 0.153) or 0.233 (95% CI: 0.219 to 0.248) when using the ATRIA versus the CHADS2 or CHA2DS2-VASc risk scores, respectively.<br>These improvements resulted mainly from downward reclassification from the CHADS2 score and entirely from downward reclassification from the CHADSVASC score. |
| Why the group were not anticoagulated | Unclear. Annualised stroke rate was 3% indicating these were not low risk patients. |

**Table 52**. Van Staa, 2011[127]

| Reference | Van Staa, 2011 [127] |
|---|---|
| Study type | Retrospective cohort study |

| Reference | Van Staa, 2011 [127] |
|---|---|
| Study sample | 79,884 patients with AF (documented record). Age 73.3, female 49.7%, 54.6% current or past smoker, CHADS score more than or equal to 3: 20%, CHF 29%, DM 17%, Hypertension 50%, previous stroke or TIA 18%. |
| Inclusion criteria | AF aged >18 in the General practice Research Database, up to warfarin or other OACs inception or INR monitoring at a mean of 2.4 years; incident and prevalent AF |
| Exclusion criteria | Rheumatic valve disease |
| Risk tools | 15 covered: see below |
| Outcome | Stroke as recorded in the GPRD, hospitalisation for stroke as recorded in the HES, and mortality resulting from stroke as recorded on death certificates. |
| Results | 79,884 strokes recorded<br>C statistics for stroke (GP recorded or registry)<br>AFI 1994: 0.60(0.58-0.61)<br>AFI 1998: 0.61(0.60-0.62)<br>ACCP 2001: 0.62(0.60-0.62)<br>ACCP2004: 0.61(0.60-0.62)<br>NICE 2006: 0.64(0.62-0.65)<br>ACC/AHA/ESC 2006: 0.64(0.62-0.66)<br>ACCP 2008: 0.64(0.62-0.65)<br>CHADSVASC (3 cats): 0.60(0.59-0.61)<br>CHADSVASC (risk score): 0.67(0.65-0.69)<br>CHADS2 (3 cats): 0.65(0.63-0.67)<br>CHADS2 (risk score): 0.66(0.64-0.68)<br>Mod CHADS2 (3 cats): 0.63(0.61-0.65)<br>Mod CHADS2 (risk score): 0.69(0.67-0.71)<br>SPAF 1995: 0.63(0.61-0.65)<br>Hart 1999: 0.62(0.60-0.64)<br>Van Walraven 2002: 0.55(0.54-0.58)<br>Van Latum1995: 0.57(0.55-0.59)<br>Framingham 2003 (3 cats): 0.62(0.60-0.64)<br>Framingham 2003 (3 cats): 0.65(0.63-0.68) |

| Reference | Van Staa, 2011 [127] |
|---|---|
| Why the group were not anticoagulated | Followed up to point of anticoagulation (2.4 years). Appears to be a cohort with normal levels of stroke risk based on CHADS score. |

**Table 53**. Wang, 2003[128]

| Reference | Wang, 2003 [128] |
|---|---|
| Study type | Developmental study with internal validation using bootstrapping. |
| Study sample | 705 participants with new onset AF (on ECG or based on hospital charts or physician office records) with no OAC treatment at baseline. Mean follow up of 4 years. |
| Inclusion criteria | Mean age 75, 48% women, SBP: 146, hypertension therapy 50%, DM 15%, smoking 18%, prior CHF or MI 34%, prior CVA/TIA 14%. |
| Exclusion criteria | AF prior to the first Framingham examination in the offspring cohort (n=1) or prior to 1960 in the original cohort (n=23); missing covariate data; stroke/TIA or death within 30 days of AF diagnosis; rheumatic mitral stenosis. |
| Risk tools | Framingham, CHADS2, SPAF 1995, AFI 1994 |
| Outcome | Stroke – decided by a panel of 3 Framingham investigators, including a neurologist, based on a review of all medical records and clinical data, and an examination by the neurologist. |
| Results | 83 strokes recorded<br>C statistics for stroke<br>Framingham:0.66 (sd=0.03) [Internal validation using bootstrapping samples]<br>CHADS2: 0.62<br>SPAF 1995: 0.62<br>AFI 1994: 0.61<br>Calibration (for Framingham only)<br>Ranking participants into quintiles according to their stroke-risk score yielded predicted 5-year stroke rates of7%(lowest quintile), 10%, 14%, 20%, and 33% (highest quintile). These predicted rates corresponded closely with actual 5-year stroke rates in each quintile: 8%, 9%, 13%, 20%, and 29%. The stroke-risk score and stroke or death–risk score had Hosmer-Lemeshow statistics of 7.6 and 6.5, respectively; values of 20 or less indicate good calibration. |
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or special group. |

1 **Table 54**. Wicke, 2019[129]

| Reference | Wicke, 2019[129] | | | |
|---|---|---|---|---|
| Study type | Retrospective cohort study | | | |
| Study sample | A broadly representative population with AF who were not on OACs from southern Germany (n=30,299). Claims data from a statutory health insurance (AOK Baden Wuerttemberg), the largest insurance fund in the German state of Baden-Wuerttemberg (population in 2014 was 10.7 million), were used. For the year 2014, the data contained information on 3.8 million individuals, which equals to about 35% of the state's population. Age 76.4; 46.6% male; CHADSVASC score 4.25; hypertension 85%; CHF 40.2%; stroke/TIA 7.96%; DM 10.1%; | | | |
| Inclusion criteria | All patients aged 18 years or older with a diagnosis of AF recorded in 2014. To increase diagnostic specificity, outpatient diagnoses of AF were required to be coded in at least two quarters of the year 2014. For hospital diagnoses, only one coding was required. Not on OACs. | | | |
| Exclusion criteria | Coded rheumatic mitral valve disease or artificial heart valves and those that died in 2014.<br>On OACs in 2014 – identified based on ATC codes of prescription data. | | | |
| Risk tools | CHADSVASC (calculated via the ICD-10 codings on the data for 2014) | | | |
| Outcome | All hospitalisations for ischaemic stroke (ICD-10 code I63) recorded on the database in 2015 and 2016. This has been downgraded for indirectness as this will have a lower prevalence than any ischaemic stroke | | | |
| Results | 961 hospitalisations due to stroke experienced by the 30,299 patients during the 2 year follow up.<br>C statistic: 0.608 | | | |
| | **Threshold** | **sensitivity** | **specificity** | |
| | ≥1 | 0.998959 | 0.0246 | |
| | ≥2 | 0.98231 | 0.088322 | |
| | ≥3 | 0.933403 | 0.17678 | |
| | ≥4 | 0.844953 | 0.317651 | |
| | ≥5 | 0.621228 | 0.528769 | |
| | ≥6 | 0.368366 | 0.752255 | |
| | ≥7 | 0.16025 | 0.910209 | |
| | ≥8 | 0.048907 | 0.977142 | |
| | ≥9 | 0.014583 | 0.993975 | |

| Reference | Wicke, 2019[129] |
|---|---|
| Why the group were not anticoagulated | Unclear but clinical data suggested this was not a low risk or a group at higher than average risk of bleeding |

**Table 55**. Xing, 2016[130]

| Reference | Xing, 2016 [130] |
|---|---|
| Study type | Retrospective cohort study from 2011 to 2013. |
| Study sample | 413 patients with NVAF, and not on oral anticoagulants for previous 6 months. mean age 81, 71% male, median CHADSVASC score 4.77. Hypertension 77.5%, previous stroke/TIA 36.8%, DM 36.1%, antiplatelets 68%. . Mean follow up 2 years. |
| Inclusion criteria | NVAF (diagnosed by 12 lead ECG or Holter), aged >65 |
| Exclusion criteria | Oral anticoagulants in past 6 months, valvular AF, rheumatic mitral stenosis, mechanical or bioprosthetic heart valves, mitral valve repair, haemodialysis. |
| Risk tools | CHADS, CHADSVASC |
| Outcome | Ischeamic stroke – new sudden focal neurological deficit resulting from a supposed CV cause that persisted >24 hours and not attributable to other causes. Brain imaging also used to differentiate from haemorrhage.<br>2 years FU |
| Results | 59 developed IS/TE<br><br>C statistics<br>CHADS2: 0.647 (0.599 – 0.693)<br>CHADSVASC: 0.615 (0.566 – 0.662)<br>De Long's test showed that CHADS2 was significantly better (NRI 0.237, p=0.0498) |
| Why the group were not anticoagulated | Unclear but not a high risk group, and no evidence that this cohort was specifically different in terms of other factors. |

**Table 56**. Xing, 2018[131]

| Reference | Xing, 2018 [131] |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 389 consecutive patients with AF (may overlap with Xing 2016). Age 83.7, 77% female, 82% hypertension, 56% vascular disease, 36% DM, 36% previous IS, 25% HF, Cr 100 mg/dL, EF 62%, CHADSVASC 4.87. Mean follow up of 2.57 years. 49 IS/TE events |
| Inclusion criteria | AF diagnosed by EMG, Holter monitoring or history. |
| Exclusion criteria | Mechanical prosthetic heart valves, PE, recent DVT and intraventricular thrombus. OACs in previous 3 months. |
| Risk tools | CHADSVASC |
| Outcome | Ischeamic stroke – new sudden focal neurological deficit resulting from a supposed CV cause that persisted >24 hours and not attributable to other causes. Brain imaging also used to differentiate from haemorrhage.<br>2.57 years |
| Results | 49 IS/TE events<br>C statistic at follow up for IS/TE:<br>CHADSVASC: 0.598 (0.513 – 0.683) |
| Why the group were not anticoagulated | Not clear but appear not to be low risk. High level of previous strokes. |

**Table 57**. Yoshizawa, 2017[65, 133]

| Reference | Yoshizawa, 2017[133] (same study as Komatsu 2014, except that Yoshizawa additionally contains results for R2CHADS as well as CHADS2 and CHADSVASC) |
|---|---|
| Study type | Retrospective cohort study |
| Study sample | 332 consecutive cases in people with paroxysmal or permanent AF (confirmed by ECG) who were not receiving anticoagulant therapy, without cardiac valvular disease estimated by TTE. Patients on rhythm control therapy. Patients not receiving OACs because this was prior to guidelines promoting their use. Followed up for mean 53 months (but up to 120 months). Age 65, male/female: 224:108, hypertension 43%, DM 13%, smoking 27%, underlying heart disease 20% (IHD 11.4%, non-ischeamic 8.6%), 18 month Hx of AF, 33% on aspirin, 0% on warfarin or other OACs. CHADSVASC score 2 points or more: 59%. |
| Inclusion criteria | See above |
| Exclusion criteria | The study excluded patients with the following conditions: severe bradyarrhythmia (sick sinus syndrome, atrioventricular block, or intraventricular conduction defect); hepatorenal dysfunction; women in whom pregnancy was likely; or patients receiving warfarin or other OACs anticoagulation therapy. |
| Risk tools | R2CHADS, CHADS VASC and CHADS2 |

| Reference | Yoshizawa, 2017[133] (same study as Komatsu 2014, except that Yoshizawa additionally contains results for R2CHADS as well as CHADS2 and CHADSVASC) |
|---|---|
| Outcome | IS/STE. Cerebral TE confirmed based on clinical symptoms and the presence of a 3mm or larger infarct area on CT/MRI.<br>Mean 53 months FU |
| Results | 2.1% rate of IS/TE per year<br>C statistic<br>R2CHADS: 0.851(0.794-0.908<br>CHADS2: 0.866(0.807-0.925)<br>CHADSVASC: 0.894(0.846-0.951) |
| Why the group were not anticoagulated | Historical reasons. Not low risk as most (59%) had CHADSVASC scores of 2 points or more. |

1

# Appendix G: Risk of bias (PROBAST)

| Study | Appropriate data sources? | Appropriate inc and exc? | Similar health across participants? | Predictors defined/ass' d same for all? | Predictor assessments made without knowledge of outcome data? | Predictors all available at time model meant to be used? | All relevant predictors analysed? | Pre-specified outcome used? | Predictors excluded from outcome definition? | Outcome defined in same way for all? | Outcome determined without knowledge of predictor information? | Reasonable number of outcome events? (100) | Time interval between baseline and outcome appropriate? (5 years) | All enrolled included in analysis? | Missing data handled appropriately? | Non:binary predictors handled appropriately? | Complexities in data accounted for? | Relevant performance measures? | Model recalibrated or likely that calibration not needed? | Overall rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abraham 2013[2] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y: 457 events | Y: up to 17 years | 2.3% lost to FU | Y | Y | Y | Y | Y | Serious |
| Abumaileq 2015a[3] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: 9 | N: 11 months | only 4/15 4 lost | Y | Y | Y | Y | Y | Very serious |
| Aspberg 2016[10] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y: 11052 | N: up to 5 years | yes | N A | Y | Y | Y | Y | Very serious |
| Chao 2016[20] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y:21008 | Y: 10 years | U | U | Y | Y | Y | Y | Serious |
| Fang 2008[27] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y: 685 | Y: 6 years | U | U | Y | Y | Y | Y | Serious |
| Fox 2017[30] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: 51 | N: 3 years | U | U | Y | Y | Y | Y | Very Serious |
| Friberg 2012b[33] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y:5359 | N: 1.4 years | U | U | Y | Y | Y | Y | Very serious |
| Gage 2001 [36] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: 94 | N: 1.2 years | U | U | Y | Y | Y | Y | Very serious |
| Gage 2004[35] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y:207 | N: 1.9 years | U | U | Y | Y | Y | Y | Very serious |

| Study | Appropriate data sources? | Appropriate inc and exc? | Similar health across participants? | Predictors defined/ass' d same for all? | Predictor assessments made without knowledge of outcome data? | Predictors all available at time model meant to be used? | All relevant predictors analysed? | Pre-specified outcome used? | Predictors excluded from outcome definition? | Outcome defined in same way for all? | Outcome determined without knowledge of predictor information? | Reasonable number of outcome events? (100) | Time interval between baseline and outcome appropriate? (5 years) | All enrolled included in analysis? | Missing data handled appropriately? | Non:binary predictors handled appropriately? | Complexities in data accounted for? | Relevant performance measures? | Model recalibrated or likely that calibration not needed? | Overall rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Guo 2013[38] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N:85 | N: 1.9 years | U | U | Y | Y | Y | Y | Very serious |
| Hippisley Cox 2013[46] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y: 890 | Y: 10 years | U | U | Y | Y | Y | Y | Serious |
| Kang 2017[57] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y: 888 | N: 1.2 years | U | U | Y | Y | Y | Y | Very serious |
| Kim 2017[63] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y: 819 | N: 4.2 years | U | U | Y | Y | Y | Y | Very serious |
| Larsen 2012[68] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: U | Y: 5.4 years | U | U | Y | Y | Y | Y | Very serious |
| Lip 2006[71] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: U | N: 1.6 years | U | U | Y | Y | Y | Y | Very serious |
| Lip 2010[72] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: U | N: 1 year | U | U | Y | Y | Y | Y | Very serious |
| Lip 2014[73] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y:273 | Y: 10 years | U | U | Y | Y | Y | Y | Serious |
| McAlister, 2017[79] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y:7,364 | N – 2.5 years | U | U | Y | Y | Y | Y | Very serious |
| McAlister, 2018[80] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y:10,827 | N – 1 years | U | U | Y | Y | Y | Y | Very serious |

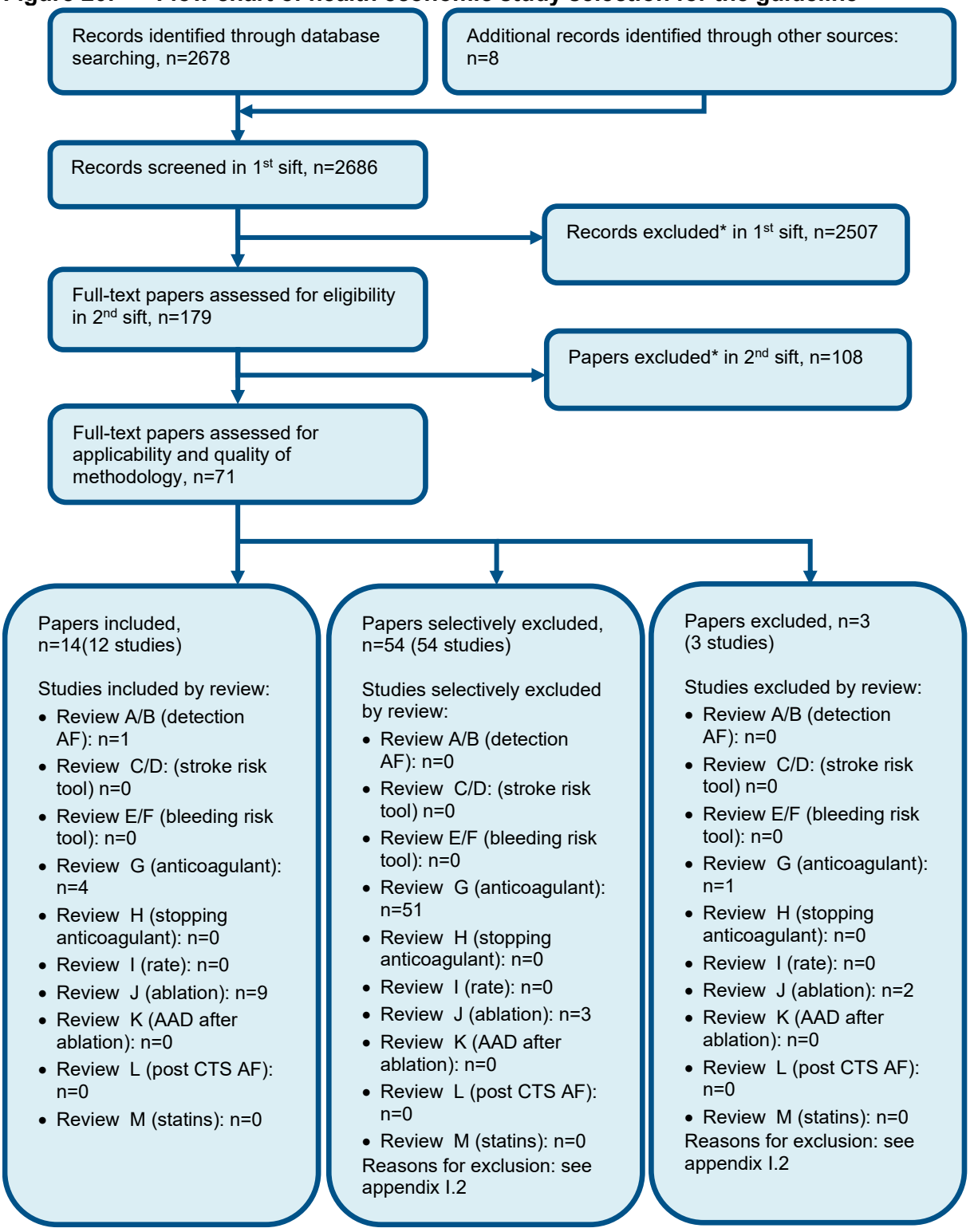
| Study | Olesen 2011[89] | Olesen 2012[88] | Olesen 2012b[90] | Singer 2013[114] | Siu 2014[115] | Suzuki 2015[118] | Tomita 2015[122] | Van dem Ham 2015[124] | Van Staa 2011[127] | Wang 2003[128] |
|---|---|---|---|---|---|---|---|---|---|---|
| Appropriate data sources? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Appropriate inc and exc? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Similar health across participants? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Predictors defined/ass' d same for all? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Predictor assessments made without knowledge of outcome data? | U | U | U | U | U | U | U | U | U | U |
| Predictors all available at time model meant to be used? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| All relevant predictors analysed? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Pre-specified outcome used? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Predictors excluded from outcome definition? | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Outcome defined in same way for all? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Outcome determined without knowledge of predictor information? | U | U | U | U | U | U | U | U | U | U |
| Reasonable number of outcome events? (100) | U but likely to be >100 | N:14 | Y: 4599 | Y: 496 | Y: 847 | N: 69 | N: 30 | Y: 3751 | Y: 1233 | N: 83 |
| Time interval between baseline and outcome appropriate? (5 years) | N: 1 year | Y: 10 years | Y: 12 years | N: 1 year | N: 3.2 years | N: 1.4 years | N: 2 years | N: 2.1 y | N: 4 years | N: 4 years |
| All enrolled included in analysis? | U | U | U | U | U | U | N | U | U | U |
| Missing data handled appropriately? | U | U | U | U | U | U | Y | U | U | U |
| Non:binary predictors handled appropriately? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Complexities in data accounted for? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Relevant performance measures? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Model recalibrated or likely that calibration not needed? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Overall rating | Very serious | Very serious | Serious | Very serious | Very serious | Very serious | Very serious | Very serious | Very serious | Very serious |

| Study | Appropriate data sources? | Appropriate inc and exc? | Similar health across participants? | Predictors defined/ass' d same for all? | Predictor assessments made without knowledge of outcome data? | Predictors all available at time model meant to be used? | All relevant predictors analysed? | Pre-specified outcome used? | Predictors excluded from outcome definition? | Outcome defined in same way for all? | Outcome determined without knowledge of predictor information? | Reasonable number of outcome events? (100) | Time interval between baseline and outcome appropriate? (5 years) | All enrolled included in analysis? | Missing data handled appropriately? | Non:binary predictors handled appropriately? | Complexities in data accounted for? | Relevant performance measures? | Model recalibrated or likely that calibration not needed? | Overall rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xing 2016[130] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N:59 | N: 2years | U | U | Y | Y | Y | Y | Very serious |
| Xing 2018[131] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N:49 | N: 2.6 years | U | U | Y | Y | Y | Y | Very serious |
| Yoshizawa 2017[133] and Komatzu, 2014[65] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N: 2.1% of 332 per year | N: 53 months | U | U | Y | Y | Y | Y | Very serious |
| Schwartz, 2019[113] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y | N | U | U | Y | Y | Y | Y | Very serious |
| Maheshwari, 2019[77] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | N | N | U | U | Y | Y | Y | Y | Very serious |
| Piccini, 2013 [93] | Y | U | U | U | U | Y | Y | Y | NA | Y | U | U | N | U | U | Y | Y | Y | Y | Very serious |
| Wicke, 2019 [129] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y | N | U | U | Y | Y | Y | Y | Serious |
| Tomasdottir, 2019[121] | Y | Y | Y | Y | U | Y | Y | Y | NA | Y | U | Y | N | U | U | Y | Y | Y | Y | Serious |

1 N=no, Y=yes, U=unclear

# Appendix H: Health economic evidence selection

**Figure 20: Flow chart of health economic study selection for the guideline**




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

# Appendix I: Economic evidence tables

None for both reviews.

# Appendix J: Excluded clinical studies

**Table 58: Studies excluded from the clinical review on the effectiveness of tools to predict stroke or thromboembolic events**

| Reference | Reason for exclusion |
|---|---|
| Guo 2017[39] | Incorrect comparison: decision tool versus usual care |
| Karlsson 2017[60] | Incorrect study design: study protocol |
| Karlsson 2018[59] | Incorrect comparison: decision tool versus usual care |
| Pandya 2018[91] | Incorrect study design: prospective cohort study |

**Table 59: Studies excluded from the clinical review on the accuracy of tools to to predict stroke or thromboembolic events**

| Study | Exclusion reason |
|---|---|
| Aakre, 2014[1] | Included anticoagulated participants |
| Abumaileq, 2015b[4] | Included anticoagulated participants |
| Al-Radeef, 2019[5] | Descriptive study – no predictive risk analysis |
| Alraies, 2017[7] | conference abstract |
| Al-Turaiki, 2016[6] | Included anticoagulated participants |
| Andersson, 2017[8] | no accuracy outcomes |
| Asberg, 2010[9] | non AF population |
| Atzema, 2015[11] | No stroke/TE outcomes |
| Banerjee, 2013[13] | conference abstract |
| Banerjee, 2013[14] | Included anticoagulated participants |
| Banerjee, 2014[12] | Included anticoagulated participants |
| Baruch, 2007[15] | Included anticoagulated participants |
| Basili, 2017[16] | Included anticoagulated participants |
| Berg,2019[17] | All patients on OACs |
| Borre, 2018[18] | SR - papers checked |
| Chan, 2016[19] | No accuracy outcomes |
| Chao, 2012[21] | no accuracy outcomes |
| Chao, 2015a[23] | Derivation study |
| Chao, 2015b[22] | no accuracy outcomes |
| Dalgaard, 2019[24] | Overall analysis used a mixture of people on and not on OACs. A sub-group analysis was performed for low risk patients (men CHADSVASC 0-1, women 0-2) who were not on OACs but this group is regarded as a special group and not representative of the overall population |
| Di Toro, 2013[25] | Non English |
| Dzeshka, 2014[26] | Review -papers checked |
| Fauchier, 2016[28] | no accuracy outcomes |
| Forslund, 2014[29] | no accuracy outcomes |
| Friberg, 2012[32] | Contained large proportion taking warfarin and analysis not stratified for warfarin/no warfarin. |
| Friberg, 2012a[31] | no accuracy outcomes |
| Friberg, 2015[34] | no accuracy outcomes |
| Gazova, 2019[37] | 86% received OACs; no relevant analyses |
| Gupta, 2012[40] | Unclear if included anticoagulated participants |
| Hippisley-Cox, 2014[47] | Not in AF population |

| Study | Exclusion reason |
|---|---|
| Hijazi, 2015[43] | conference abstract |
| Hijazi, 2016[44] | Included anticoagulated participants |
| Hijazi, 2016[45] | conference abstract |
| Hijazi, 2016a[42] | Included anticoagulated participants |
| Hijazi, 2017[41] | Included anticoagulated participants |
| Holt,2018[48] | Not a predictive risk analysis study |
| Horne, 2019[49] | 11% on warfarin with no sub-grouping |
| Hu, 2018[50] | Unclear if anticoagulated |
| Huang, 2017[51] | prediction of left atrial thrombus |
| Inohara, 2017[52] | Included anticoagulated participants |
| Inoue, 2006[53] | no accuracy outcomes |
| Jaakkola, 2018[54] | no accuracy outcomes |
| Jaakola, 2018[54] | No relevant outcomes; mixture of people on and off OACs |
| Joundi, 2016[55] | SR |
| Kabra, 2016[56] | Included anticoagulated participants |
| Kang, 2017[58] | Most of the sample without AF |
| Kearon,2019[61] | Commentary on Berg, 2019 |
| Kim, 2015[62] | Included anticoagulated participants |
| Kim, 2017b[64] | no accuracy outcomes |
| Komatsu, 2012[66] | no accuracy outcomes |
| Laguna, 2005[67] | no accuracy outcomes |
| Larsen, 2011[69] | conference abstract |
| Lin,2018[70] | No predictive analyses undertaken; Insufficient data to calculate predictive measures (numbers of people at each CHADSVASC score given, but not proportion of these with stroke. Incidence density (strokes per 100 person-years) given for stroke but cannot use this to extrapolate numbers with stroke as the incidence density may be confounded by a person having > 1 stroke. |
| Lip, 2013[75] | Included anticoagulated participants |
| Lip, 2014[74] | Valvular AF |
| Lowres,2019[76] | SR and meta-analysis |
| Masaki, 2009[78] | Included anticoagulated participants |
| Naccarelli, 2012[81] | Included anticoagulated patients |
| Nakagawa, 2011[82] | No accuracy outcomes |
| Ntaios, 2019[84] | Prediction of mortality, not stroke |
| O'Brien, 2015[85] | conference abstract |
| Oldgren, 2016a[86] | conference abstract |
| Oldgren, 2016b[87] | Included anticoagulated participants |
| Parsons,2018[92] | Non AF population |
| Piyaskulkaew, 2014[94] | No stroke/TE outcome; population limited to CHADS 0-1 |
| Poli, 2011[98] | Included anticoagulated participants |
| Poli, 2014[97] | No accuracy outcomes |
| Poli, 2017[96] | Included anticoagulated participants |
| Poli,2009a[95] | Included anticoagulated participants |
| Potpara, 2012[99] | Included anticoagulated participants |
| Potpara, 2012[100] | Included anticoagulated participants |
| Proietti, 2018[101] | SR |

| Study | Exclusion reason |
|---|---|
| Puurunen, 2014[102] | Population undergoing percutaneous coronary intervention |
| Rietbrock, 2008[103] | Included anticoagulated participants |
| Rivera-Caravaca, 2017[106] | conference abstract |
| Rivera-Caravaca, 2017b[105] | bleeding risk study |
| Rivera-Caravaca, 2018[107] | Included anticoagulated participants |
| Rivera-Caravaca, 2018[107] | All patients on VKAs |
| Rivera-Caravaca,2017a[104] | Included anticoagulated participants |
| Roldan, 2018[108] | Included anticoagulated participants |
| Ruff, 2016[109] | Included anticoagulated participants |
| Ruiz-Ortiz, 2010 [110] | Included anticoagulated participants |
| Sander Van Doorn, 2018[111] | SR - references checked |
| Somme, 2010[116] | Included anticoagulated participants and no accuracy outcomes |
| Sun, 2019[117] | No predictive outcomes |
| Tanaka, 2015[119] | Outcomes were severity of stroke in a cohort who all had stroke |
| Tanaka, 2018[120] | Included anticoagulated participants |
| Tsai, 2014[123] | Included anticoagulated participants |
| Van Den Ham, 2014[125] | conference abstract |
| Van Mieghem, 2017[126] | Review; All patients on VKAs |
| Yang, 2018[132] | Included anticoagulated participants |
| Zhu, 2017[134] | SR - references checked |

# Appendix K: Excluded economic studies

Studies that meet the review protocol population and interventions, and the economic study inclusion criteria but have not been included in the review based on applicability and/or methodological quality are summarised below with reasons for exclusion.

**Table 60: Studies excluded from the health economic review**

| Reference | Reason for exclusion |
|---|---|
| None for both reviews | |

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