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CONTEMPORARY REVIEW

Risk Stratification Tools to Guide a Personalized Approach for Cardiac Monitoring in Embolic Stroke of Undetermined Source

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ABSTRACT: Current recommendations support a personalized sequential approach for cardiac rhythm monitoring to detect atrial fibrillation after embolic stroke of undetermined source. Several risk stratification scores have been proposed to predict the likelihood of atrial fibrillation after embolic stroke of undetermined source. This systematic review aimed to provide a comprehensive overview of the field by identifying risk scores proposed for this purpose, assessing their characteristics and the cohorts in which they were developed and validated, and scrutinizing their predictive performance. We identified 11 risk scores, of which 4 were externally validated. The most frequent variables included were echocardiographic markers and demographics. The areas under the curve ranged between 0.70 and 0.94. The 3 scores with the highest area under the curve were the Decryptoring (0.94 [95% CI, 0.88–1.00]), newly diagnosed atrial fibrillation (0.87 [95% CI, 0.79–0.94]), and AF-ESUS (Atrial Fibrillation in Embolic Stroke of Undetermined Source) (0.85 [95% CI, 0.80–0.87]), of which only the latter was externally validated. Risk stratification scores can guide a personalized approach for cardiac rhythm monitoring after embolic stroke of undetermined source.

Key Words: AF-ESUS ■ atrial fibrillation ■ Decryptoring ■ ESUS ■ ischemic stroke ■ NDAF

In about 17% of all patients with ischemic stroke, no cause is identified despite the recommended diagnostic workup.[1] These strokes are classified as embolic strokes of undetermined source (ESUS), a term that is not synonymous with the broader term cryptogenic stroke, because the latter also includes patients with incomplete diagnostic workup, as well as those who have multiple potential causes.[2,3] The potential causes of stroke in a patient with ESUS may include supracardiac atherosclerosis, left atrial disease, left ventricular disease, right-to-left shunt, cardiac valvular disease, and others.[2,3]

Atrial fibrillation (AF) is a frequently detected finding during the diagnostic workup of ESUS, with incidence ranging between 2% at 1 week after stroke and up to 30% at 3 years.[4] Although AF was initially considered as the main underlying mechanism of ESUS, accumulating evidence shows that this causal association is weaker than was previously hypothesized.[4,5] Current recommendations support a personalized, sequential, and stratified approach for cardiac rhythm monitoring for AF detection in patients with ESUS.[5–7] Specifically, after the initial cardiac rhythm monitoring for 24 to 72 hours, patients are selected for prolonged cardiac

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Nonstandard Abbreviations and Acronyms

AF-ESUS	Atrial Fibrillation in Embolic Stroke of Undetermined Source
ASSERT	Subclinical Atrial Fibrillation and the Risk of Stroke
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
ESUS	embolic stroke of undetermined source
NAVIGATE ESUS	Rivaroxaban for Stroke Prevention After Embolic Stroke of Undetermined Source
NDAF	newly diagnosed atrial fibrillation
RE-SPECT ESUS	Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source
TRENDS	The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk

rhythm monitoring based on the likelihood of covert AF.[5–8] In this context, several risk scores have been proposed to stratify the risk of covert AF and thereby assist individualization of the diagnostic workup of ESUS and guide clinical decisions about cardiac rhythm monitoring in this patient population.

This systematic review aimed to provide a comprehensive overview of the field. We sought to identify all published risk scores through a systematic review, assess their characteristics and the cohorts in which they were developed and validated, and scrutinize their predictive performance. The information summarized in this review can be useful to treating physicians in selecting the optimal tool for individualization of clinical practice decisions pertinent to cardiac rhythm monitoring in patients with ESUS.

METHODS

The data that support the findings of this study are available in the supplementary material of this article.

Registration and Search Strategy

This systematic review is registered at PROSPERO (International Prospective Register of Systematic Reviews; unique identifier: CRD42022381886).

We systematically reviewed the literature for published scores proposed for the identification of AF in patients with ESUS. We searched MEDLINE, Scopus, Cochrane Library, Google Scholar, and the ClinicalTrials registry from inception until October 2022. The detailed search strategy that we followed for each individual database is available in Table S1, and individual studies were screened using the predetermined inclusion criteria. The search was conducted by 2 independent reviewers (A.M.L., K.P.), blinded to each other, and any disagreements were resolved by discussion with a third reviewer (G.N.) and consensus.

Eligibility Criteria

We included both prospective and retrospective studies that described either the derivation of an original risk score or the external validation of a previously published risk score. For a study to be included, the performance of the risk score assessed in the form of diagnostic accuracy, specificity, and sensitivity should have been reported. We excluded studies that reported only predictors of AF rather than a structured risk score, or were not reported in the English language, or were not published as full texts. Studies were screened for eligibility using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (flow diagram outlining the screening process [Figure S1] and checklist are presented in Table S1).[9] Reference lists of eligible studies were reviewed to screen for additional relevant observational or randomized studies.

Data Extraction

Data were extracted independently by 2 investigators (A.M.L., K.P.) and cross-checked blindly with each other. Disagreements were reviewed by 2 other reviewers (A.T.A., S.N.) and resolved by discussion and consensus. From the eligible studies that met inclusion criteria, we extracted data about (1) study characteristics, (2) population characteristics, (3) the components of the individual clinical risk scores, and (4) the performance indices of the scores. The study characteristics abstracted included author/study group name, name of the clinical risk score assessed, year of publication, study size, study duration including follow-up, study type, stroke type, definition of AF and its onset, and

mode of ECG monitoring used. Population characteristics extracted included mean age, sex, mean National Institutes of Health Stroke Scale at baseline, mean modified Rankin Scale at baseline, comorbidities, and mean left atrial diameter visualized on echocardiography. Population characteristics were extracted from both the original derivation cohort and internal and external validation cohorts.

Descriptive statistics are presented as percentages for categorical variables and as means for continuous variables. To evaluate the performance of each risk score, the area under the curve (AUC) (or C statistic) and 95% CI were extracted and compared for discriminative ability or their overall performance.

Quality and Risk of Bias Assessment

The risk of bias for all included studies was independently assessed by 2 investigators (A.M.L., K.P.), blind to one another, using the Quality Assessment of Diagnostic Accuracy Studies-2 tool.[10] Any disagreement was resolved by discussion and consensus with the addition of a third independent investigator (G.N.). As a part of quality and risk of bias assessment, studies were evaluated under 4 individual domains: patient selection, index test, reference standard, and flow and timing. All domains addressed the risk of bias, whereas the first 3 domains evaluated applicability. Quality assessment of individual studies (Quality Assessment of Diagnostic Accuracy Studies-2 tool) is detailed in Figure S2.

RESULTS

Search Results

The literature search identified 8169 studies for review. After screening titles and abstracts, 73 studies were selected for full-text evaluation. Ultimately, 11 studies evaluating 11 risk scores fulfilled the eligibility criteria and were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining the screening methodology is included in Figure S1.

Study and Population Characteristics

Overall, 11 studies with a total of 9984 patients were included in the systematic review.[11–21] The characteristics of included studies are detailed in Table 1.[11–21] The characteristics of the population included in each study are presented in Table 2.[11–21] Mean age reported in 10 out of 11 studies ranged from 63.1 to 81.4 years, and men constituted 41.5% to 61.9% of the individual study populations. The definition of AF varied between individual studies. Although any AF was considered significant in some cohorts,[12,13,15,19,22] others defined it as AF lasting >30 seconds[14,17,18,20] or ≥30 seconds.[11,16] The mode and duration of cardiac rhythm monitoring was largely variable between studies, including 24- to 48-hour monitoring with a Holter or telemetry device,[11,14,15,17,22] Holter device for up to 4 weeks,[12,14,19,20] and implantable loop recorders.[14,16,18] Similarly, there were large differences in the duration of follow-up, ranging from 15 days[17] to >5 years.[13]

Components of the Risk Scores

The most frequent parameters used as components of the risk scores were echocardiographic markers including left atrial diameter,[12,15,16,19,20,23] left atrial area ≥16 cm^2,[11] left atrial volume index,[18] reduced left ventricular ejection fraction,[16,23] valvular heart disease,[12,13] left ventricular hypertrophy,[23] left ventricular end-diastolic volume <65 mL,[12] left atrial conduit strain <10.4%,[17] and left atrial reservoir strain <25.3%.[17] Demographic characteristics such as age were included by all studies with the exception of the PROACTIA (Prediction of occult atrial fibrillation in patients after cryptogenic stroke and transient ischemic attack) score.[18] Age categories considered to be significant varied between studies, ranging from ≥60 years[23] to ≥75 years.[13,24] Several comorbidities were incorporated in the scores, including hypertension,[13,17,19,23] history of stroke,[11,16,19] recurrent stroke on antiplatelets or multiterritory brain infarct,[16] nonstenotic carotid plaque,[23] coronary artery disease,[11,13,19] peripheral artery disease,[13,19] congestive heart failure,[13] obesity (body mass index >30 kg/m^2),[13] hypercholesterolemia,[12] chronic obstructive pulmonary disease or obstructive sleep apnea,[20] and thyroid disease.[20] Stroke characteristics that formed key components of the clinical risk prediction score included stroke severity assessed by the National Institutes of Health Stroke Scale score,[15,19] absence of vascular cause of stroke,[15] presence of intracranial large vessel occlusion,[20] cortical stroke,[20] subcortical infarct,[19,23] and presence of a posterior lesion.[19] Electrocardiographic parameters included in the scores were supraventricular extrasystoles,[16,18,23] atrial runs,[16] and P-wave morphology and duration.[18] Laboratory markers included were N-terminal pro-B-type natriuretic peptide[16,17,20] and troponin.[17] The components of individual risk-prediction scores are detailed in Table 3[11–21] and graphically represented as a Venn diagram in Figure 1.[11–21]

Assessment of the Performance of the Risk Scores

Among the 11 risk scores, the Decryptoring,[17] newly diagnosed atrial fibrillation (NDAF),[11] and AF-ESUS (Atrial Fibrillation in Embolic Stroke of Undetermined Source) scores[21] had the highest AUCs: 0.94 (95% CI, 0.88–1.00), 0.87 (95% CI, 0.79–0.94), and 0.85 (95% CI, 0.79–0.86), respectively. The performance of each

Table 1. Characteristics of the Studies That Proposed the Risk Scores

Study	Year of publication	Study period	Study type	Stroke type	AF definition	Mode of ECG monitoring	Follow-up period
ACTEL[12]	2020	2007–2017	Retrospective	IS/CS	Any AF	Continuous ECG monitoring for ≥5 d	NA
AF-ESUS[21]	2020	NA	Retrospective	IS/CS	Any AF	Any ECG performed during the follow-up period for any reason, including palpitations, irregular pulse on clinical examination, in-hospital surveillance with Holter monitoring, or portable outpatient monitoring	>12 mo
Brown ESUS-AF[14]	2018	2013–2016	Retrospective	IS/CS	AF >30 s	24-h continuous telemetry monitoring, 30-d cardiac monitor, ILR	36 mo
Decryptoring score[17]	2021	2019–2020	Prospective	IS/CS	AF >30 s	Continuous in-hospital ECG monitoring ≥48 h and ambulatory Holter monitoring for 15 d	15 d
E2AF[19]	2022	2017–2020	Retrospective	IS/CS	Any AF	ECG monitoring using a nonimplantable external event recorder for 2 wk	90 d
Graz AF[16]	2021	2018–2019	Prospective	IS/CS	AF ≥30 s	Pulse control, in-hospital continuous rhythm monitoring, ECG monitoring triggered by patient symptoms and/or clinical suspicion, ILR	>12 mo
HAVOC[13]	2017	1995–2015	Retrospective	IS/TIA/CS	Any AF	NA	>5 y
NDAF[11]	2013	2006–2007	Prospective	IS/TIA/CS	AF ≥30 s	Holter monitoring provoked by evaluation during outpatient visits, standard ECG during outpatient follow-up visits at 6 mo, 12 mo, and annually	>2 y
PROACTIA[18]	2022	2016–2018	Prospective	IS/CS	AF >30 s	Implantable cardiac monitors	833 (633–1028) d
SAFE[20]	2022	2018–2021	Prospective	IS/TIA/CS	AF >30 s	In-hospital telemetry monitoring, 28-d Holter monitoring, routine visits	12 mo
STAF[15]	2019	2014–2015	Retrospective	IS/CS	Any AF	12-lead ECG, 24-h continuous telemetry monitoring, Holter monitoring in the previous 3 mo	3 mo

ACTEL indicates Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium; AF, atrial fibrillation; AF-ESUS, Atrial Fibrillation in Embolic Stroke of Undetermined Source; CS, cryptogenic stroke; ESUS, embolic stroke of undetermined source; E2AF, The Empoli ESUS Atrial Fibrillation; HAVOC, Hypertension, Age, Valvular heart disease, peripheral Vascular disease, Obesity, Congestive heart failure, Coronary artery disease; ILR, implantable loop recorder; IS, ischemic stroke; NA, not applicable; NDAF, newly diagnosed atrial fibrillation; PROACTIA, Prediction of occult atrial Fibrillation in patients after cryptogenic stroke and transient ischemic attack; SAFE, the screening for atrial fibrillation scale; STAF, Score for the Targeting of Atrial Fibrillation; and TIA, transient ischemic attack.

Table 2. Characteristics of the Cohorts Used for the Development of the Risk Scores

Characteristic	ACTEL[12]	AF-ESUS[21]	Brown ESUS-AF[14]	Decryptoring score[17]	E2AF[19]	Graz AF[16]	HAVOC[13]	NDAF[11]	PROACTIA[18]	SAFE[20]*	STAF[15]
External validation	No	Yes	Yes	No	No	No	Yes	No	No	No	Yes
Size, n	110	839	298	63	82	150	7671	164	236	460	133
Age, mean±SD†	69.7±13.4	67±22.5	63.9±14.8	77.7±7.8	72±10	66.7±15.3	56.7%	65.4±15.1	68.6±12.5	65±13.4	63.1±15
Female sex, %	56.4	43.1%	47.3	55.6	58.5	43.3	49.9	48	38	33	45.1
Baseline NIHSS, mean±SD	6.7±6	6±10	3.6±4.3	NA	2.13±2.74	8.7±16.5	NA	3.3±4	NA	5±5.2	5.1±3.1
Baseline mRs, mean±SD	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	1.3±0.7
Hypertension, %	79.1	62.2	71.1	60.3	80.5	66.6	56.7	60	63.6	60	62.4
Dyslipidemia, %	72.7	65.9	52.7	60.3	NA	48.0	NA	35	NA	41.5	36.8
Diabetes, %	15.5	18.5	26.8	22.2	21.6	16.0	21.6	23	30	24.8	38.3
Smoking, %	23.6	38.6	24.8	17.5	NA	24.0	NA	25	28	52.2	15.8
Previous stroke/TIA, %	NA	16.9	30.2	NA	NA	10.6	NA	15	NA	13.5	24.8
Coronary artery disease, %	NA	15.2	16.8	NA	1.581	NA	1.581	16	NA	7.2	16.5
Chronic kidney disease, %	NA	NA	NA	NA	2.4	NA	2.4	24	NA	8.9	NA
Peripheral artery disease, %	NA	2.9	NA	NA	8.6	NA	8.6	8	NA	NA	0.8
Valvular heart disease, %	54.5 (MR), 33.6 (TR)	0.6	NA	NA	7.5	NA	7.5	0	NA	6.7	54.9 (MR), 23.3 (AI)
LA diameter, mm	41.0±6	NA	35.7±6.5	36.4±7.4	NA	NA	NA	35.8±5.8	NA	NA	NA

ACTEL indicates Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium; AF, atrial fibrillation; AF-ESUS, Atrial Fibrillation in Embolic Stroke of Undetermined Source; AI, aortic insufficiency; ESUS, embolic stroke of undetermined source; E2AF, The Empoli ESUS Atrial Fibrillation; HAVOC, Hypertension, Age, Valvular heart disease, peripheral Vascular disease, Obesity, Congestive heart failure, Coronary artery disease; NA, not applicable; NDAF, newly diagnosed atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale; PROACTIA, prediction of occult atrial fibrillation in patients after cryptogenic stroke and transient ischemic attack; SAFE, the screening for atrial fibrillation scale; STAF, Score for the Targeting of Atrial Fibrillation; MR, mitral valve regurgitation; mRs: modified Rankin scale; TIA, transient ischemic attack; and TR, tricuspid valve regurgitation.

*The demographics from the SAFE study represent its entire study population, which includes patients who did not meet the criteria for ESUS.

† All values indicate mean age, except the HAVOC score, which indicates percent of individuals >75 years old.

Table 3. Characteristics of the Risk Scores

Characteristic	ACTEL[12]	AF-ESUS[21]	Brown ESUS-AF[21]	Decryptoring score[17]	E2AF[19]	Graz AF[16]	HAVOC[13]	NDAF[11]	PROACTIA[18]	SAFE[20]	STAF[15]
Range of the score	−1 to 4	−9 to 8	0 to 4	0 to 44	0 to 14	0 to 16	0 to 14	0 to 6	NA	0 to 10	0 to 8
Proposed threshold for clinical use	≥2	>0	NA	>10	>10	≥4	≥4	>1	NA	≥5	≥5
Variables included in the scores	• Age • Hypercholesterolemia • LA size • LVEDV • Tricuspid regurgitation	• Age • Hypertension • LV hypertrophy • LA diameter • LVEF • Any supraventricular extrasystole • Subcortical infarct • Nonstenotic carotid plaque	• Age • Moderate–severe LA enlargement	• Age • Hypertension • Troponin levels • NT-proBNP levels • LA strain reservoir • LA strain conduit	• Age • NIHSS • Hypertension • Cortical and/or subcortical lesion • Posterior lesion • LA enlargement • Coronary artery disease and/or peripheral artery disease	• Age • Prior cortical/cerebellar infarction • LVEF • LA enlargement • Supraventricular premature beats (baseline ECG) • Atrial run • NT-proBNP levels • Recurrent stroke on antiplatelets or multiterritory brain infarct	• Age • Coronary artery disease • Valvular heart disease • Hypertension • Peripheral artery disease • Obesity • Congestive heart failure	• Age • Coronary artery disease • Previous stroke • LA size	• Atrial premature beat • P-wave morphology • LA volume index • P-wave duration	• Age • COPD or OSA • Thyroid disease • NT-proBNP levels • LA enlargement • Cortical topography of stroke • Intracranial large vessel occlusion	• Age • NIHSS • LA dilation • Absence of vascular cause

ACTEL indicates Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; ESUS, embolic stroke of undetermined source; E2AF, The Empoli ESUS Atrial Fibrillation; HAVOC, Hypertension, Age, Valvular heart disease, Obesity, Congestive heart failure, Coronary artery disease; LA, left atrium; LV, left ventricle; LVEDV, left ventricularle end-diastolic volume; LVEF, left ventricularle ejection fraction; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSA, obstructive sleep apnea; PROACTIA, Prediction of occult atrial Fibrillation in patients after cryptogenic stroke and transient ischemic attack; SAFE, the screening for atrial fibrillation scale; and STAF, Score for the Targeting of Atrial Fibrillation.

risk score along with the cohorts in which they were evaluated is detailed in Table 4[11–21] and graphically represented as a forest plot in Figure 2.[11,12,15–19,21]

External Validation of the Risk Scores

Among the 11 risk scores, 4 were externally validated: the AF-ESUS, Brown ESUS-AF, STAF (Score for the Targeting of Atrial Fibrillation), and HAVOC (Hypertension, Age, Valvular heart disease, Obesity, Congestive heart failure, Coronary artery disease) scores.[13–15,23] The AF-ESUS score was externally validated in 123 patients with ESUS and had a sensitivity of 80% for the AF-ESUS threshold ≤0 to detect AF episodes lasting >6 hours.[25] Both Brown ESUS-AF[14] and STAF[15] were validated in 191 patients with an AUC of 0.70 (95% CI, 0.62–0.78) and 0.71 (95% CI, 0.63–0.79), respectively.[12] The HAVOC score was validated in 2 cohorts of 214 and 658 patients with an AUC of 0.68 (95% CI, 0.62–0.73) in the latter cohort.[26,27]

DISCUSSION

This systematic review identified 11 risk scores that have been proposed as a tool for the stratification of the likelihood of AF detection in patients with ESUS. We identified significant heterogeneity in the components of the risk scores, because 48 different parameters have been included overall. Also, we found heterogeneity in the extent of external validation, because only 4 risk scores were externally validated. Additionally, there was heterogeneity in the predictive performance of the scores, with an AUC range of between 0.70 and 0.94. The 3 scores with the highest AUC were the Decryptoring, NDAF, and the AF-ESUS scores, of which only the latter was externally validated.[11,17,21]

Almost every study included in this systematic review identified patient age as a powerful predictor of AF.

The NDAF score defined age ≥72 years as an independent predictive factor.[11] HAVOC, ACTEL (Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium), and the Decryptoring score used an age threshold of ≥75 years.[12,13,17] Graz AF included age >75 years in its major criteria and age 60 to 75 years in its minor criteria.[16] Additionally, the AF-ESUS score used an age threshold of ≥60 years.[21] Age ≥65 years was associated with a higher risk of AF also at the Empoli ESUS-AF score, SAFE (the screening for atrial fibrillation scale) score, and Brown ESUS-AF score.[14,19,20] The STAF score adds 2 points to every patient >62 years old. PROACTIA was the only score that did not use age as a compound.[15,18]

All scores excluded, except HAVOC, identified echocardiographic variables as some of the strongest predictors of AF. Left atrial size was the dominant

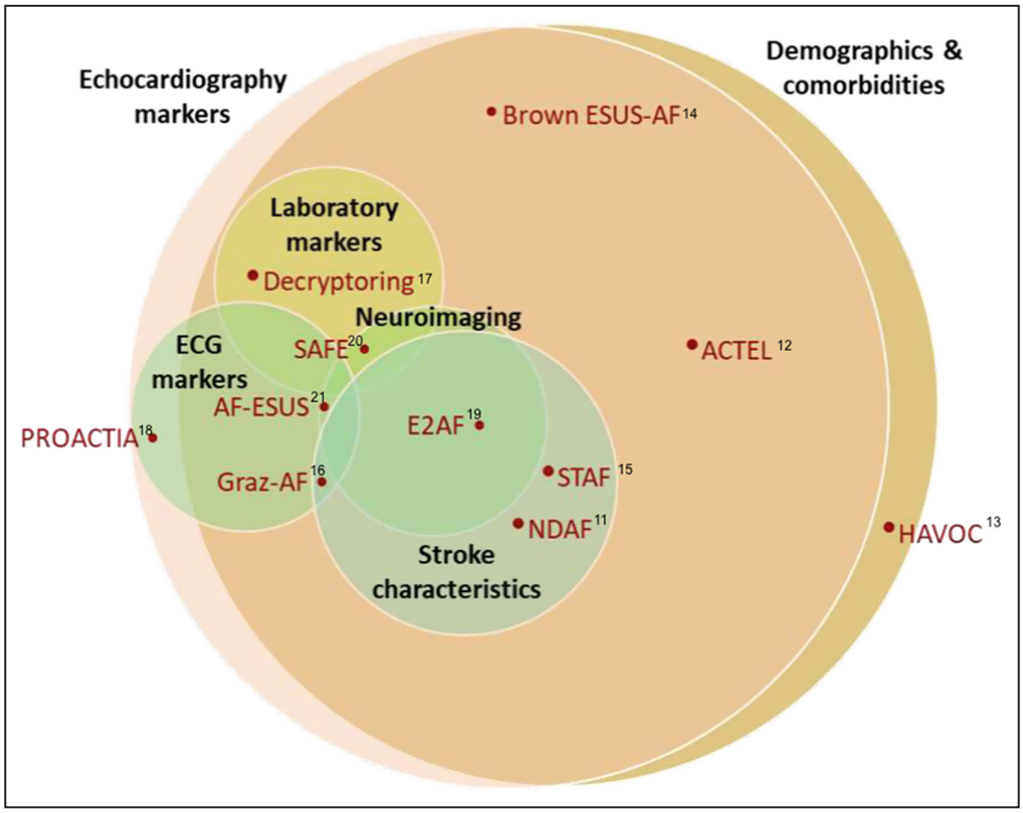

Figure 1. Venn diagram of clinical risk score components.
The diagram presents the variable categories included by the clinical risk scores. The radius of each circle corresponds to the number of times the category is included by the risk scores. The union represents the overlap of these categories between studies. Demographics and comorbidities include age, coronary artery disease, peripheral artery disease, heart failure, hypertension, valvular disease, obesity, hypercholesterolemia, chronic obstructive pulmonary disease, obstructive sleep apnea, thyroid disease, and nonstenotic carotid plaque. Stroke characteristics include previous stroke, National Institutes of Health Stroke Scale, recurrent stroke on antiplatelets or multiterritory brain infarct, and vascular cause. Neuroimaging includes posterior or cortical and/or subcortical lesion, and intracranial large vessel occlusion. ECG includes supraventricular extrasystoles, P-wave duration and/or morphology, and atrial runs. Laboratory markers include N-terminal pro-B-type natriuretic peptide levels and troponin levels. Echocardiography includes LV ejection fraction, LA size, LV end-diastolic volume, LV hypertrophy, LA strain conduct, LA strain reservoir, and LA volume index. ACTEL indicates Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium; AF, atrial fibrillation; AF-ESUS, Atrial Fibrillation in Embolic Stroke of Undetermined Source; ESUS, embolic stroke of undetermined source; E2AF, The Empoli ESUS Atrial Fibrillation; HAVOC, Hypertension, Age, Valvular heart disease, Obesity, Congestive heart failure, Coronary artery disease; LA, left atrial; LV, left ventricular; NDAF, newly diagnosed atrial fibrillation; PROACTIA, Prediction of occult atrial fibrillation in patients after cryptogenic stroke and transient ischemic attack; SAFE, the screening for atrial fibrillation scale; and STAF, score for the targeting of atrial fibrillation.

covariate included in STAF, NDAF, Graz AF, AF-ESUS, Brown ESUS-AF, SAFE, and Decryptoring scores.[11,14–17,20,21] Reduced left ventricular ejection fraction was also associated with higher risk of AF with varying thresholds; the Graz AF included left ventricular ejection fraction <40% among the major risk criteria and left ventricular ejection fraction 40% to 50% among the minor risk criteria, and the AF-ESUS score set the threshold at left ventricular ejection fraction <35%.[16,21] The Decryptoring score also used left atrial strain reservoir <25.3% and left atrial strain conduct <10.4%, which is in line with recent evidence showing that left atrial strain is a strong predictor at AF in patients with ESUS.[17,28]

Atrial Fibrillation Is Frequently Detected Among Patients With ESUS

AF is a frequent finding in patients with ESUS, with the estimate ranging according to the intensity of cardiac rhythm monitoring. In the Athens Stroke Registry, AF was detected in 29.1% of all patients with ESUS. In the RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy

Table 4. Assessment of Performance of Clinical Risk Scores

Study	Derivation and validation	Cohort	Size (n)	C statistic AUC (95% CI)	Sensitivity/specificity at best thresholds
ACTEL[12]	Derivation cohort (Muscari et al)	SOMH20	191	0.80 (0.73–0.87)	0.56/0.93
AF-ESUS[21]	Derivation cohort (Ntaios et al)	ASTRAL, ASR, LSR	839	0.85 (0.79–0.86)	0.95/NPV: 0.98
	Internal validation (Ntaios et al)	ASTRAL, ASR, LSR		0.84 (0.8–0.87)	
	External validation (Kitsiou et al)	EKB	123	NA	For AF episodes >6 min: 0.77/ NPV: 0.65 For AF episodes >6 h: 0.80/ NPV: 0.84 For AF episodes >10 h: 1.00/ NPV: 1.00
Brown ESUS-AF[14]	Derivation cohort (Ricci et al)	WAMSBU	296	0.73 (NA)	0.63/0.71[a]
	External validation cohort (Muscari et al)	SOMH20	191	0.70 (0.62–0.78)	NA
Decryptoring score[17]	Derivation cohort (Vera et al)	HULP	63	0.94 (0.88–1.00)	0.83/0.66
E2AF[19]	Derivation cohort (Grifoni et al)	SGH	82	0.75 (0.64–0.84)	0.75/0.70
Graz AF[16]	Derivation cohort (Kneihsl et al)	GSU	854	0.85 (0.78–0.92)	0.92/0.67
HAVOC[13]	Derivation cohort (Kwong et al)	STRIDE	7671	0.77 (NA)	0.55/0.82
	Validation cohort (Zhao et al)	CRYSTAL AF	214	NA (NA)	0.35/0.83
	Validation cohort (Ntaios et al)	ASTRAL, ASR, LSR	658	0.68 (0.62–0.73)	0.77/NA
NDAF[11]	Derivation cohort (Bugnicourt et al)	AUH	166	0.87 (0.79–0.94)	NA
PROACTIA[18]	Derivation cohort (Skrebelyte-Strøm et al)	AkUH	236	0.79 (0.73–0.86)	NA
SAFE[20]	Derivation cohort (Pascasio et al)	TUH	227	0.82 (NA)	0.83/0.80
STAF[15]	Derivation cohort (Goksu et al)	ARTH	133	0.70 (0.59–0.80)	0.86/0.71
	External validation cohort (Muscari et al)	SOMH20	191	0.71 (0.63–0.79)	NA

ACTEL, Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium; AF, atrial fibrillation; AkUH, Akershus University Hospital; ARTH, Antalya Research Training Hospital; ASR, Athens Stroke Registry; ASTRAL, Acute Stroke Registry and Analysis of Lausanne; AUC, area under the curve; AUH, Amiens University Hospital; CRYSTAL-AF, Cryptogenic Stroke and Underlying Atrial Fibrillation; EKB, Evangelisches Klinikum Bethel; ESUS, embolic stroke of undetermined source; E2AF, The Empoli ESUS Atrial Fibrillation; GSU, Graz Stroke Unit; HAVOC, Hypertension, Age, Valvular heart disease, Obesity, Congestive heart failure, Coronary artery disease; HULP, Hospital Universitario de La Princesa; LSR, Larissa Stroke Registry; NA, not applicable; NDAF, newly diagnosed atrial fibrillation; NPV, negative predictive value; SGH, San Giuseppe Hospital; PROACTIA, Prediction of occult atrial fibrillation in patients after cryptogenic stroke and transient ischemic attack; SAFE, the screening for atrial fibrillation scale; SOMH, Saint Orosola-Meldipighi Hospital 2020; STAF, score for the targeting of atrial fibrillation; STRIDE, Stanford Translational Research Integrated Database Environment; TUH, Torrecárdenas University Hospital; and WAMSBU, Warren Alpert Medical School of Brown University.

[a]For a score=2.

and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source) trial, 7.5% of patients were found to develop AF reported as an adverse event or using cardiac monitoring per standard clinical care during a median follow-up of 19 months.[29] In a meta-analysis of 47 studies and 8215 patients with ESUS or cryptogenic stroke, the rate of AF detection by implantable cardiac monitoring ranged between 2% at 1 week after stroke and 28.5% at 36 months.[4]

AF Detected After ESUS: How Strong Is the Causal Association?

There is a growing amount of evidence that suggests that the causal association of AF detected after ESUS is weaker than initially considered. For example, in the ASSERT (Subclinical Atrial Fibrillation and the Risk of Stroke) and TRENDS (The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk) studies, the majority of embolic events did not occur proximal to recent episodes of atrial tachycardia or fibrillation.[30,31] In addition, the rate of AF detection was similar between patients with ESUS and non-ESUS stroke in the AF-Randomized study.[32]

Moreover, the negative results of the NAVIGATE ESUS (Rivaroxaban for Stroke Prevention After Embolic Stroke of Undetermined Source) and RE-SPECT ESUS trials, in which rivaroxaban and dabigatran, respectively, did not reduce stroke rates compared with aspirin, point to the same direction; if AF was a major cause of ESUS, it could be expected that they would show reduced stroke rates compared with aspirin in these 2 trials. Considering the striking benefit of apixaban in reducing the risk of stroke compared with aspirin in patients with AF in the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial,[33–35] the results of NAVIGATE ESUS and RE-SPECT ESUS do not support the hypothesis of strong causal association between AF and ESUS.

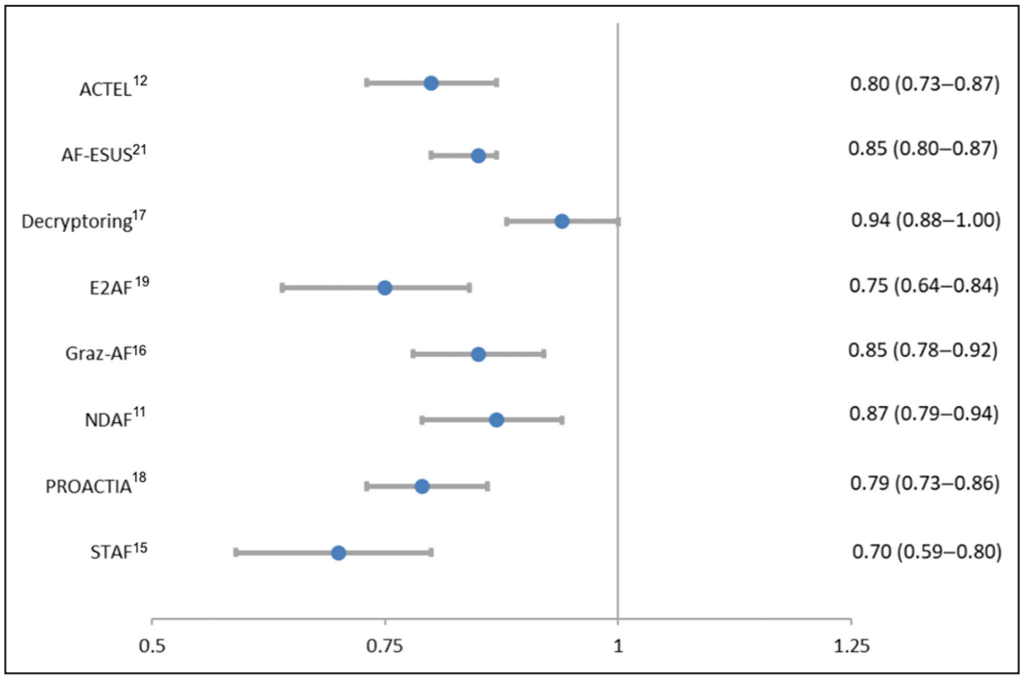

Figure 2. Areas under the curve of the risk scores for the prediction of AF.
The forest plot summarizes the performance of each risk score in predicting the likelihood of AF after ESUS using the calculated area under the curve and the corresponding 95% CI. ACTEL indicates Age, Cholesterol, Tricuspid, End diastolic volume, Left atrium; AF: atrial fibrillation; AF-ESUS, Atrial Fibrillation in Embolic Stroke of Undetermined Source; ESUS, embolic stroke of undetermined source; E2AF, The Empoli ESUS Atrial Fibrillation; PROACTIA, Prediction of occult atrial fibrillation in patients after cryptogenic stroke and transient ischemic attack; and STAF, score for the targeting of atrial fibrillation.

It is hypothesized that the more proximal an AF episode is to the index stroke, and the longer it lasts, the more likely it is that there is a causal association.[5] On the other hand, episodes that are chronologically distant from the ESUS or are of short duration might be irrelevant in regard to cause.[5] The hypothesis that AF episodes of shorter duration are only weakly associated with ESUS, if at all, is also supported by the results of the NOAH-AFNET-6 (Non vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes) trial, which evaluated the potential benefit of oral anticoagulation in patients with atrial high-rate episodes. The trial was terminated prematurely due to an observed trend toward futility for efficacy combined with expected safety concerns, which weakens the putative causal association of short episodes of AF with ESUS.[36]

Should We Screen All Patients With ESUS for AF? Choosing the Right Candidate Wisely

Based on the aforementioned evidence and as suggested by current recommendations and consensus statements, a sequential stratified approach seems rational, in which prolonged cardiac rhythm monitoring is reserved only for a subgroup of patients with ESUS with specific characteristics that indicate a higher likelihood of covert AF.[5–8,37] The use of risk scores in clinical practice to stratify the risk of covert AF of our patients with ESUS and select the best candidates for prolonged cardiac rhythm monitoring is a rational choice. The availability of several noninvasive and invasive modalities for AF screening, including patient-initiated oscillometric blood pressure monitors, handheld devices, smartwatches, wearable nonadhesive dry-electrode belts, adhesive patch devices, and implantable loop recorders, extends our ability to individualize further our approach in patients with ESUS.[7]

Limitations

A limitation of this systematic review is the variety of definitions of AF used in the included studies. Five scores defined AF as any recorded episode, whereas the rest of the scores used a definition of continuous detected AF for ≥30 seconds or more. The methods for detection of AF also differed between the included studies. Holter monitoring, routine visits with ECGs, and implantable loop recorders were mainly used for AF detection with a follow-up period range between 15 days and >5 years. Another limitation of this review is we do not have access to prognostic covariates at the level of individual patient data. Therefore, there is

no accurate statistical method that can be used to examine the impact of each particular covariant.

CONCLUSIONS

This systematic review identified several risk scores that have been proposed as tools to stratify patients with ESUS according to their likelihood of AF detection. The 3 scores with the highest AUC were the Decryptoring, NDAF, and the AF-ESUS scores, of which only the latter was externally validated. These tools can guide individualized clinical practice decisions about prolonged cardiac rhythm monitoring in patients with ESUS.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figures S1–S2

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Supplemental Material

Table S1. Database search.

Databases searched	Search terms
MEDLINE	(exp Embolic Stroke/ OR exp Ischemic Stroke/ OR cryptogenic stroke.mp. OR embolic stroke of undetermined source.mp.) AND (exp Atrial Fibrillation/ OR atrial fibrillation.mp.) AND (predicts.mp OR score.mp. OR exp Risk Assessment/ OR risk.mp.)
Scopus	(TITLE-ABS-KEY ("cryptogenic stroke" OR "stroke of un* source" OR "stroke of un* cause" OR "stroke of un* origin" OR "stroke of un* etiology")) AND (TITLE-ABS-KEY ("atrial fibrillation")) AND (TITLE-ABS-KEY (scor* OR predict* OR risk)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))
Google Scholar	Score AND "atrial fibrillation" AND "cryptogenic stroke" OR "embolic stroke of undetermined source" OR "stroke of unknown source" OR "stroke of unknown cause"
Cochrane Library	"cryptogenic stroke" OR "embolic stroke of undetermined source" OR ESUS in Title Abstract Keyword AND "atrial fibrillation" in Title Abstract Keyword AND scor* OR predict* OR risk* in Title Abstract Keyword

Clinical Trials Registry	"cryptogenic stroke" OR "embolic stroke of undetermined source" |Atrial Fibrillation |score

Figure S1. PRISMA flow diagram of screening methodology.

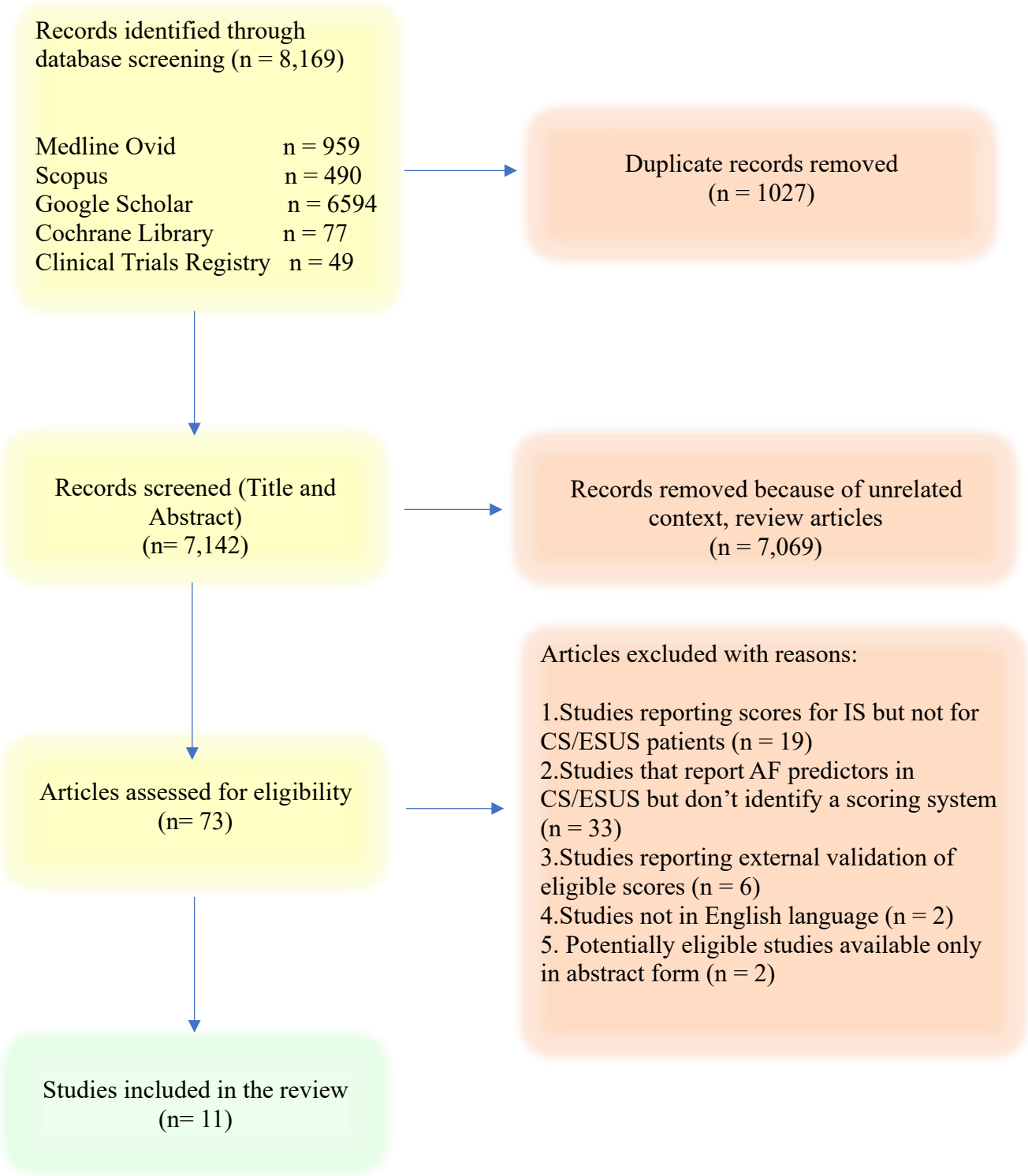

Figure S2. Risk of bias assessment using the QUADAS-2 tool (Quality Assessment of Diagnostic).

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
ACTEL[12]	−	+	?	?	−	+	?
AF-ESUS[21]	+	+	−	−	+	+	?
BROWN ESUS-AF[14]	+	+	+	+	+	+	+
Decryptoring[17]	?	+	+	+	?	+	+
E2AF[19]	+	+	+	+	+	+	+
GRAZ-AF[16]	+	?	−	−	+	?	?
HAVOC[13]	−	+	+	?	−	+	−
NDAF[11]	+	+	+	+	+	+	+
PROACTIA[18]	+	+	+	+	+	+	+
SAFE[20]	−	+	+	+	+	+	+
STAF[15]	?	+	+	+	?	+	?

Low Risk − **High Risk** ? **Unclear Risk**