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Prediction of atrial fibrillation after a stroke event: A systematic review with meta-analysis

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ABSTRACT

BACKGROUND Detecting atrial fibrillation (AF) after stroke is a key component of secondary prevention, but indiscriminate prolonged cardiac monitoring is costly and burdensome. Multivariable prediction models could be used to inform selection of patients.

OBJECTIVE This study aimed to determine the performance of available models for predicting AF after a stroke.

METHODS We searched for studies of multivariable models that were derived, validated, or augmented for prediction of AF in patients with a stroke, using MEDLINE and Embase from inception through September 20, 2024. Discrimination measures for tools with C statistic data from ≥3 cohorts were pooled by bayesian meta-analysis, with heterogeneity assessed through a 95% prediction interval. The risk of bias was assessed with the Prediction model Risk Of Bias Assessment tool (PROBAST).

RESULTS We included 75 studies with 58 prediction models; 66% had a high risk of bias. Fifteen multivariable models were eligible for meta-analysis. Three models showed excellent discrimination: SAFE (C statistic, 0.856; 95% confidence interval [CI], 0.796–0.916), SURF (0.815; 95% CI, 0.728–0.893), and iPAB (0.888; 95% CI, 0.824–0.957). Excluding high-bias studies, only SAFE showed excellent discrimination (0.856; 95% CI 0.800–0.915). No model showed excellent discrimination when limited to external validation or studies with ≥100 AF events. No clinical impact studies were found.

CONCLUSION Three of the 58 identified multivariable prediction models for AF after stroke demonstrated excellent statistical performance on meta-analysis. However, prospective validation is required to understand the effectiveness of these models in clinical practice before they can be recommended for inclusion in clinical guidelines.

KEYWORDS Atrial fibrillation; Prediction; Stroke; Prevention; AF

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Introduction

Atrial fibrillation (AF)–related strokes exhibit a high rate of recurrence and are associated with substantial morbidity, long-term disability, and mortality.[1–3] Initiation of appropriate secondary prevention anticoagulation in patients identified with underlying AF after an acute stroke event may prevent recurrent stroke and reduce mortality.[4,5] Because AF is often paroxysmal and asymptomatic, it may not be detected with

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short-term monitoring and may require extended cardiac monitoring.[6–9]

Multivariable prediction models could identify stroke patients without known AF who are at higher risk of undiagnosed AF, enabling a more personalized and cost-effective approach to selection of those for extended cardiac monitoring. Previous reviews have considered the prediction of AF after stroke but have failed to conduct a meta-analysis[10,11] or to include validation studies,[10] limiting the generalizability of the findings. Even when meta-analysis has been performed, the absence of sensitivity analyses calls into question the robustness of findings.[11]

To address this knowledge gap, we conducted a systematic review of multivariable prediction models for incident AF after a stroke and performed a quantitative synthesis of performance to determine whether any may be suitable for clinical use.

Methods

Search strategy and inclusion criteria

We searched all articles in Embase and MEDLINE databases (Ovid platform) from inception to September 20, 2024. Full details of the search strategy are available in the Supplemental Materials. For a study to be eligible for inclusion, it had to be an original study in human adults (≥18 years of age) that developed or validated a multivariable model for the prediction of AF in patients with a stroke or transient ischemic attack (TIA) and excluded patients with AF at baseline.

All identified articles were uploaded onto the Rayyan systematic review web application.[12] Four investigators (A.H., K.R., T.Y., W.G.) independently screened the articles for inclusion by looking through their titles, abstracts, full text, and supplemental material. Any disagreements were resolved by discussion with the fifth and sixth investigators (E.R. and R.N.). Artificial intelligence tools aided screening but were not used for data extraction. This review was registered on PROSPERO (CRD42024523250) and informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (Supplemental Materials).[13,14]

Abbreviations

AF: atrial fibrillation

AUROC: area under the receiver operating characteristic curve

CI: confidence interval

ECG: electrocardiogram

NRI: net reclassification improvement

PI: prediction interval

PROBAST: Prediction model Risk Of Bias Assessment Tool

TIA: transient ischemic attack

Data extraction and quality assessment

Two independent investigators (A.H. and R.N.) extracted data and assessed each model's risk of bias and applicability using Prediction model Risk Of Bias Assessment Tool (PROBAST).[15] Discrepancies between reviewers were resolved through group discussions.

Discrimination measures were extracted to quantify the predictive performance of the tools.[16] We extracted data on the area under the receiver operating characteristic curve (AUROC) or the C statistic and the associated 95% confidence intervals (CIs). When the 95% CI was not reported in the study, we calculated it by previously described methods.[17] We also extracted calibration metrics and, for studies on model augmentation, data on discrimination performance, the net reclassification improvement (NRI) index, and integrated discrimination improvement. We searched for clinical utility data through decision curve analysis or decision analytical modeling. In addition, forward citation searches were conducted to identify studies on the impact of these models in clinical practice.

Data synthesis and statistical analysis

Numerical variables were reported as mean ± standard deviation or median with the interquartile range. Statistical significance was set at .05. We assessed the C statistic or AUROC for individual studies and defined a positive NRI with a 95% CI excluding 0 as an improvement in augmented models. For studies with multiple cohorts, we assessed tool performance for each cohort separately. We generated funnel plots and calculated Egger test[18] to check for publication bias.

We carried out a bayesian meta-analysis to assess discrimination using a summary measure of the C statistics and corresponding 95% CIs (Supplemental Materials). We also calculated the 95% prediction interval (PI) to portray the degree of heterogeneity between studies and to suggest a potential spectrum for the prediction models' performance in a new validation.[17] Bayesian methods were chosen because unlike frequentist approaches, they use structured probability models to quantify uncertainty in parameter estimates.[16,19,20] These methods are useful in dealing with sparse data and substantial between-study variability or when PIs are required as they allow a more accurate representation of uncertainty in parameter estimates compared with frequentist methods.[16] Research has shown that frequentist methods can produce unreliable CIs and PIs, especially when study sizes vary.[21,22] Summary C statistics were defined a priori on the basis of prior literature,[23,24] as follows: <0.60, inadequate; 0.60 to 0.69, adequate; 0.70 to 0.79, acceptable; and >0.80, excellent.

We performed the meta-analyses in R using the metafor and metamisc packages (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria).[25]

Our primary meta-analysis evaluated the overall discrimination for predictive tools with C statistic data from 3 or more cohorts.[24,26,27] We then performed analyses to check the sensitivity of our methods based on subsets of studies: those reporting external validation results, those with a low or unclear risk of bias in PROBAST, studies reporting >100 events, and studies with >100 events and low or unclear risk of bias in PROBAST.

Results

Study selection

We found 8125 unique reports, reviewed 184 full-text records, and included 75 studies (Figure 1). The Supplemental

Materials lists studies that were excluded but met several inclusion criteria.

Characteristics of included studies

The included studies assessed multivariable prediction models in 82 cohorts (Supplemental Tables S1 and S2). Of the cohorts, 33 (40.2%) included patients with ischemic strokes, 13 (15.9%) included those with either ischemic stroke or TIA, 17 (20.7%) included only cases of cryptogenic stroke or embolic stroke of undetermined source, another 7 (8.4%) included cryptogenic stroke or TIA, and 12 (14.6%) included patients with stroke without further phenotypic characterization (Supplemental Table S2).

The number of included participants ranged from 48 to 392,155, with a mean age and percentage of women ranging from 43.0 years to 77.5 years and 25.2% to 55.3%, respectively. The number of incident AF cases per study ranged from 7 to 21,103, with 71% (n = 60) reporting fewer than 100 events.

Characteristics of included prediction models

The included studies represented data on 58 unique multivariable prediction models. Of the multivariable prediction models, 3 used only electrocardiogram (ECG) variables, 19 used only clinical variables, and 36 used a combination of modalities (Supplemental Tables S3–S8). Age was the most frequently used clinical variable (77%), followed by

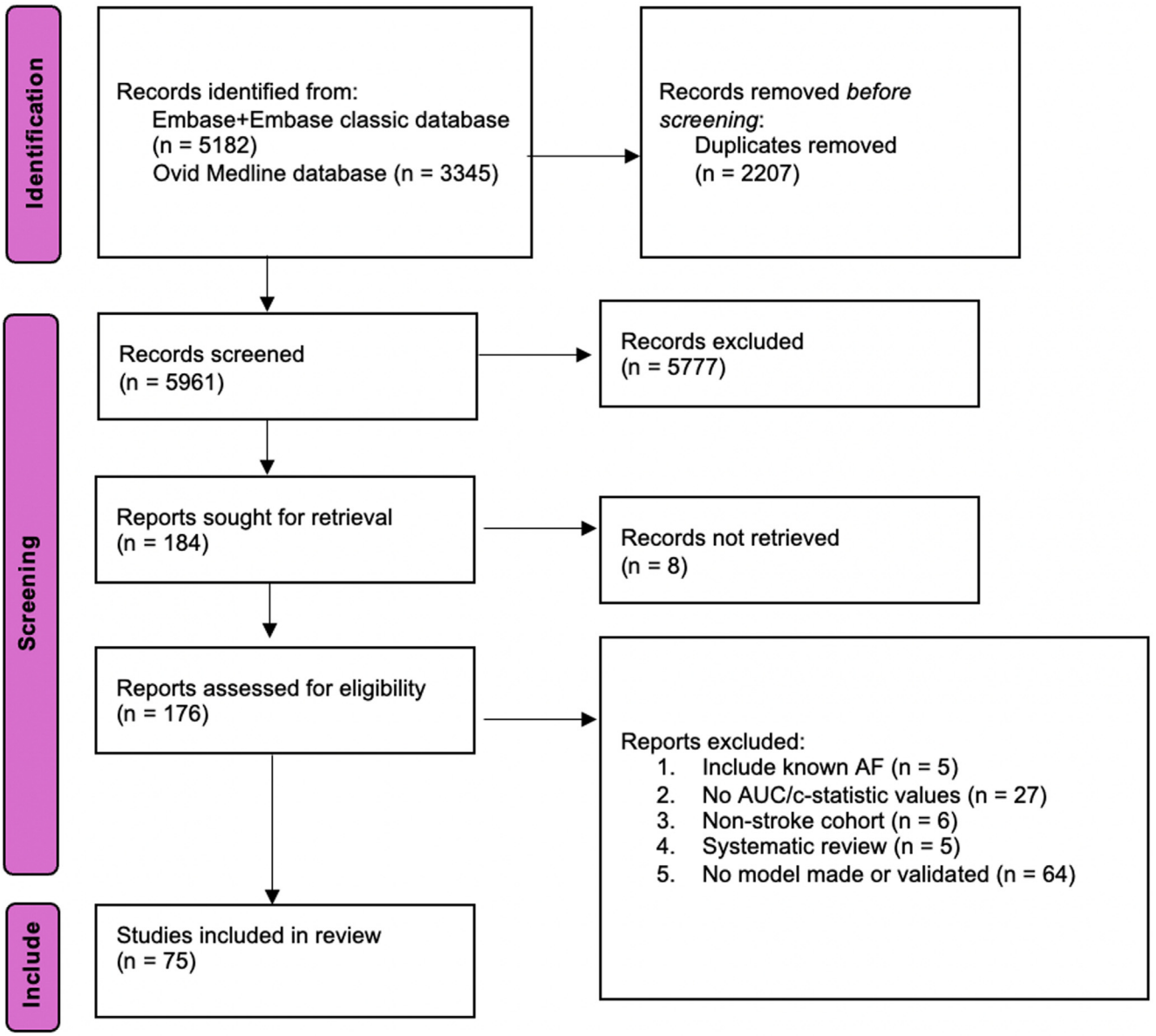

Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the paper selection process for this systematic review. AF = atrial fibrillation; AUC = area under the receiver operating characteristic curve.

hypertension (43%) and heart failure (37%; Figure 2). Eight multivariable prediction models originally developed for other purposes were evaluated for prediction of AF after a stroke (Supplemental Table S9).

Model performance

All studies reported a measure of discrimination, with reported C statistics or AUROCs ranging from 0.511 (95% CI, 0.442–0.580)[28] to 0.990 (95% CI, 0.853–0.999)[29] (Supplemental Table S10). Only 23 of 58 (40%) models had calibration estimated, and 30 (52%) models were externally validated, with 12 (21%) externally validated in >1 other data set.

Clinical utility and clinical impact

None of the included studies assessed clinical utility, and no studies on the clinical impact of the prediction models were found through a forward citation search.

Model augmentation

Fifteen studies conducted augmentation of a multivariable prediction model (Supplemental Table S11). Stroke severity improved the prediction performance for 3 models: CHA_2DS_2-VASc (NRI of 57.6%; 95% CI, 49%–63.3%), $CHADS_2$ (NRI of 57.6%; 95% CI, 50.4–64.7%), and HATCH (NRI of 50.6%; 95% CI, 43.5%–57.7%).[30]

Risk of bias assessment

Overall, 66% of results had a high risk of bias (Figure 3), mainly because of issues in the analysis domain (65%), such as lack of calibration performance and improper handling of missing data.

Meta-analysis

Fifteen multivariable prediction models were eligible for meta-analysis. Of the multivariable prediction models, 5 models were previously developed for different indications (C_2HEST, $CHADS_2$, CHA_2DS_2-VASc, CHARGE-AF, HATCH) and 10 models were designed specifically for predicting AF after a stroke (AS5F, BROWN ESUS-AF, CHASE-LESS, HAV-OC, iPAB, LADS, RE-CHARGE AF, SAFE, STAF, SURF).

Despite high heterogeneity, 3 models developed for AF after a stroke demonstrated excellent discriminative performance (SAFE, summary C statistic, 0.856 [95% CI, 0.796–0.916]; SURF, 0.815 [95% CI 0.728–0.893]; iPAB, 0.888 [95% CI 0.824–0.957]), 1 model was just below the threshold for excellent performance (STAF, summary C statistic, 0.792 [95% CI, 0.704–0.873]), and 4 other models showed acceptable summary discrimination performance (AS5F, summary C statistic, 0.739 [95% CI, 0.717–0.761]; CHASE-LESS, 0.734 [95% CI, 0.71–0.760]; LADS, 0.713 [95% CI, 0.538–0.881]; RE-CHARGE AF, 0.705 [95% CI, 0.642–0.0.785]; Figure 4). None of the models originally derived for another purpose but validated for prediction of AF after a stroke achieved better than adequate discriminative performance (Figure 5).

In our sensitivity analysis, the exclusion of studies at high risk of bias left only the SAFE model with excellent discrimination performance (summary C statistic, 0.856 [95% CI, 0.800–0.915]; Supplemental Figure S1). In restricting analyses to either external validation results or studies with >100 AF events, no model had excellent discrimination performance (Supplemental Figures S2–S4). In restricting analyses to only studies with >100 AF events and a low or uncertain risk of bias, only the CHASE-LESS model (summary C statistic, 0.738 [95% CI, 0.712–0.767]) had adequate discrimination performance (Supplemental Figure S4). The funnel plot was symmetric (Egger test $P = .45$; Supplemental Figure S5) but

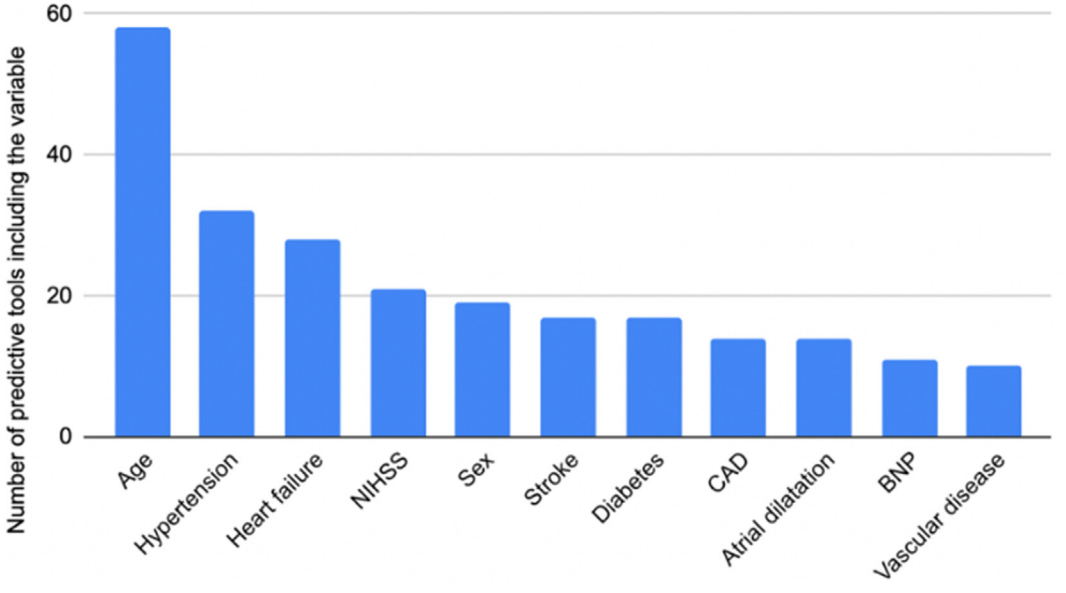

Figure 2
Overview of the 10 most common predictors in risk models for AF after stroke. BNP = B-type natriuretic peptide; CAD = coronary artery disease; NIHSS = National Institutes of Health Stroke Scale score.

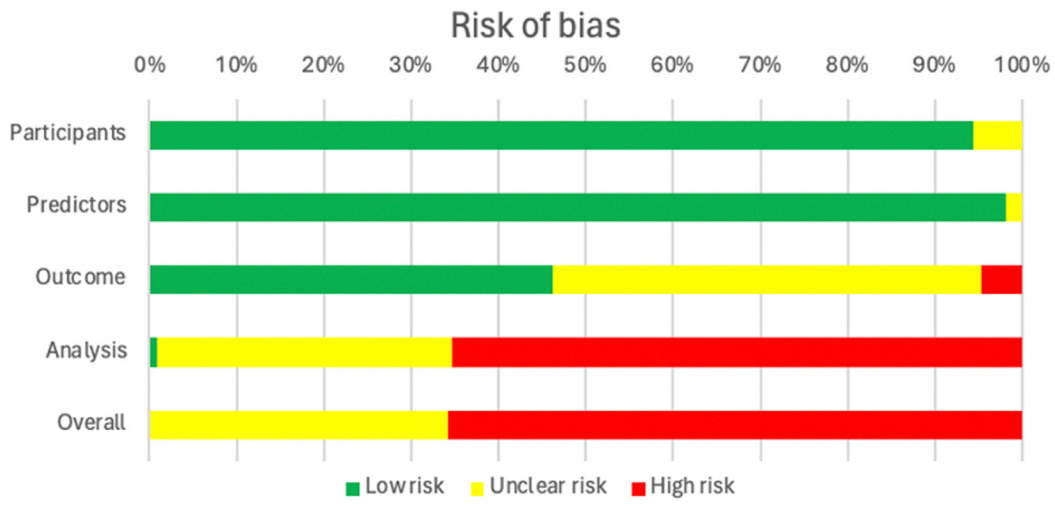

Figure 3
Risk of bias of included studies to the review question. Judgments on the 3 Prediction model Risk Of Bias Assessment Tool (PROBAST) applicability domains are presented as percentages across all included studies.

with additional scatter consistent with the presence of between-study heterogeneity.

Discussion

This systematic review and meta-analysis provides an overview of 58 different multivariable prediction models to estimate patients' risk of having AF detected after a stroke. In the meta-analysis, 3 multivariable risk prediction models—SAFE, SURF, and iPAB—showed excellent discrimination performance for AF after stroke. However, studies were often at high risk of bias or included fewer than 100 AF events. On sensitivity analysis, prediction performance measures were not robust and prospective validation was absent, suggesting that their clinical utility is unproven.

Previous work

Consistent with previous reviews, we identified suboptimal model development practices[31] and a lack of progression to have an impact on studies for risk scores.[24,32] Previous reports have summarized multivariable prediction models but lacked a quantitative synthesis of discrimination performance, limiting their utility in identifying the best models for clinical use.[10,11] Furthermore, previous reviews lacked sensitivity analyses, potentially inflating their pooled performance estimates.[10,33,34] Unlike previous studies, our analysis incorporated prediction models developed with machine learning and artificial intelligence techniques.[10,11,31] Notably, on most occasions, these models did not consistently outperform those based on traditional regression methods. Our quantitative synthesis and sensitivity analysis provide deeper insights into the performance and generalizability of multivariable prediction models for AF after a stroke event.

Clinical relevance

In ischemic stroke survivors, the European Society of Cardiology recommends class IIa long-term ECG monitoring with noninvasive monitors or implanted loop recorders,[35] whereas US guidelines include a class IIa indication for an insertable cardiac monitor in patients with cryptogenic stroke when external ambulatory monitoring is inconclusive.[36] In routine clinical practice, long-term ECG monitoring is now commonly used after presentation with ischemic stroke. Evidence from randomized clinical trials and observational studies shows that extended cardiac monitoring after stroke doubles AF detection and anticoagulation rates compared with shorter monitoring durations.[37–39] However, even when an implantable loop recorder is placed in patients with an ischemic stroke, most patients are not diagnosed with AF,[40] leading to cost and patient burden. Risk stratification could make this process more efficient and cost-effective for health care systems.

The SAFE, SURF, and iPAB models showed excellent discrimination performance, although this was not robust in sensitivity analysis. In addition, they require the determination of B-type natriuretic peptide levels, which may not be standard in post-stroke pathways. In contrast, the CHASE-LESS model showed adequate discrimination after excluding biased studies or those with few events and used only clinical variables routinely available in stroke care. The BROWN-ESUS AF and HAVOC scores were recommended by the ESC Working Group on e-Cardiology[41] but did not perform best in this meta-analysis.

Beyond multivariable models, other approaches have been investigated to predict AF after a stroke. In a small study, a higher probability of AF by artificial intelligence–enabled ECG, a deep neural network trained on sinus rhythm 12-lead ECGs, was associated with AF detection on ambulatory rhythm monitoring in patients after a stroke.[42] A subanalysis of the FIND-AF$_{RANDOMIZED}$ clinical trial suggested that use of B-type natriuretic peptide to select patients for prolonged monitoring could reduce the number needed to screen from 18 to 3.[43]

However, without clinical impact studies or decision curve analyses, it remains uncertain whether implementing these

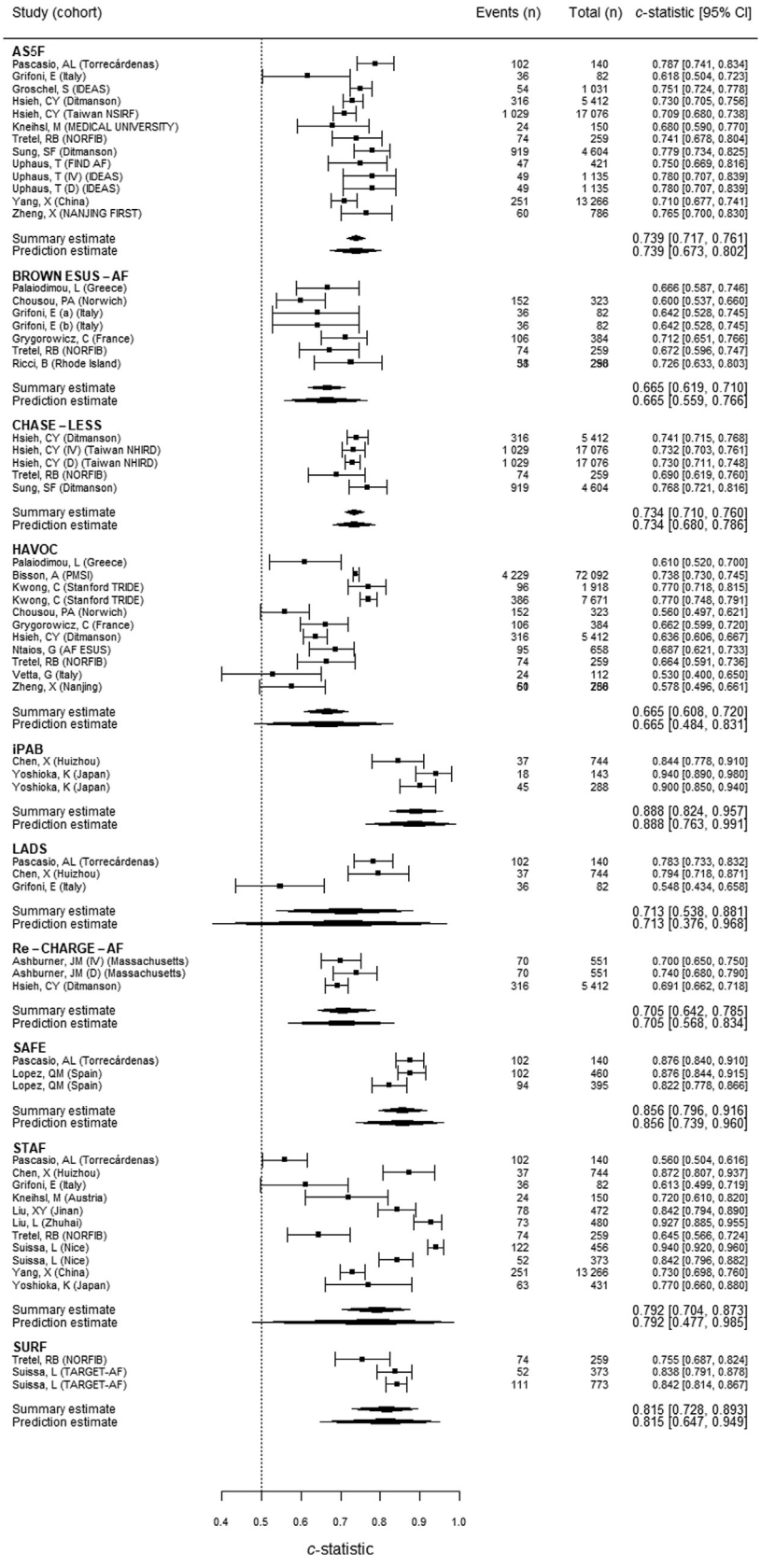

Figure 4
Forest plot of models developed for the prediction of atrial fibrillation after stroke. CI = confidence interval.

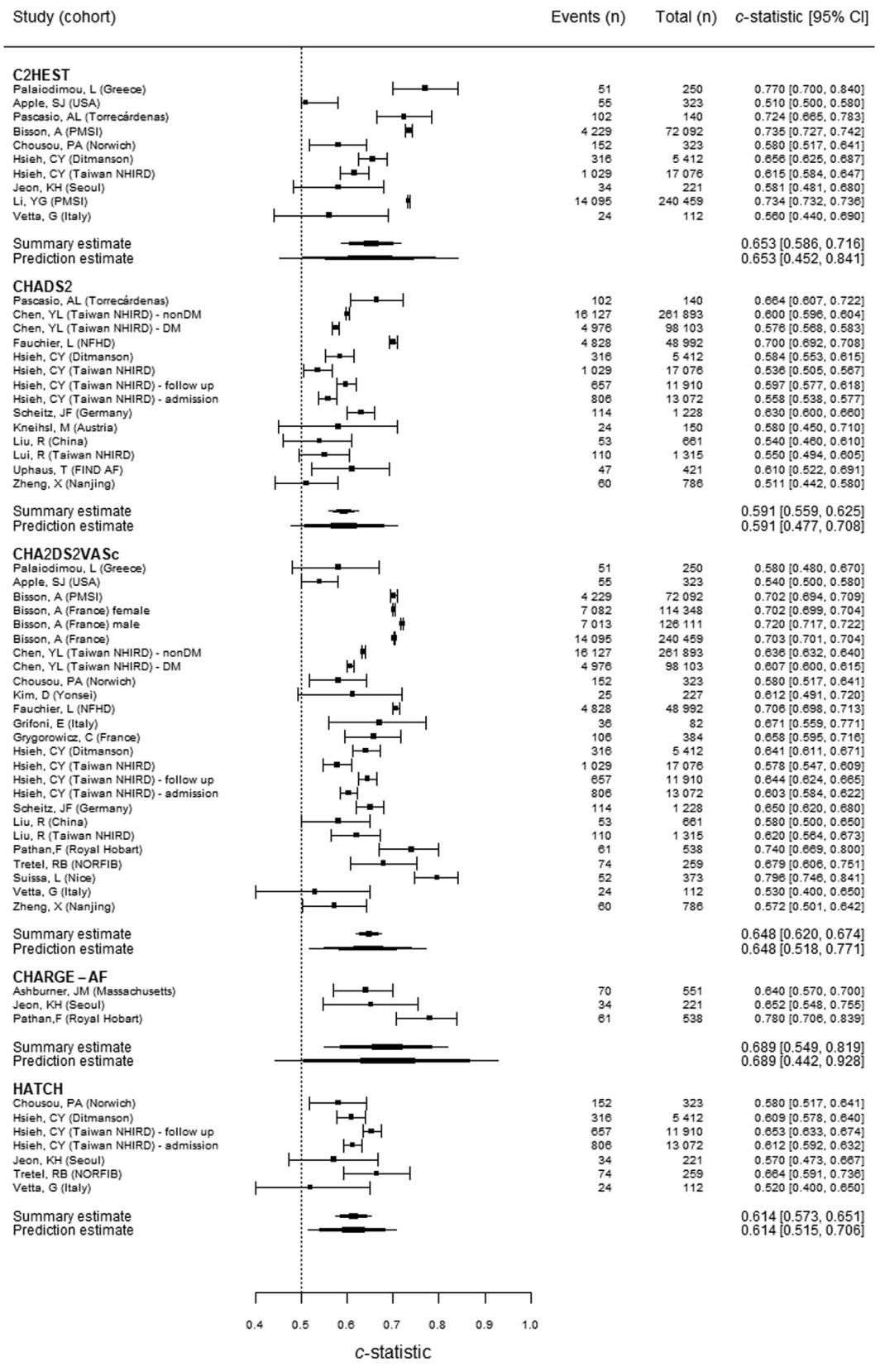

Figure 5
Forest plot of models developed for other indications but used to predict atrial fibrillation after stroke. CI = confidence interval.

multivariable prediction models will increase the yield of AF detected during extended monitoring. Furthermore, prospective studies and piloting are essential to establish the positive predictive value and negative predictive value of these models in clinical practice and the optimal thresholds to be used for ruling in patients for extended monitoring (for which high specificity would be prioritized).[44] Therefore, more data are needed on how these models should be implemented in clinical practice before they can be recommended for inclusion in clinical guidelines.

Strengths and limitations

We used a comprehensive search strategy and thorough analysis involving experts in cardiology and neurology. We included any multivariable prediction model for predicting AF after stroke, broadening our scope to models not originally designed for this outcome but with potential merits.

However, we acknowledge our study's limitations. First, the prediction models included in the analyses are derived and validated in vastly different populations regarding participant characteristics, the underlying stroke risk, and the prevalence of the various risk factors that influence the probability of AF detection or AF occurrence and used different methods for AF detection. We included both prospective and retrospective cohort studies, which may introduce bias as AF is often asymptomatic, and detection rates in routine care may be lower than in scheduled prospective investigations.[45] We included studies that had cohorts with varying stroke phenotypes, which may have affected the AF event rates between studies.[46] Variability in stroke causes can have an impact on the occurrence of AF detection after a stroke,[7] although prolonged searches for AF have been demonstrated to improve AF detection rates in both ischemic stroke and cryptogenic stroke.[40,47]

We did not perform meta-regression or subgroup meta-analysis because of the absence of individual patient data, as such analyses could be prone to ecologic bias,[48] and individual participant data meta-analysis was outside the scope. In addition, we could not analyze model calibration performance because of a lack of relevant studies.

Conclusion

In this systematic review and meta-analysis, 3 multivariable prediction models had excellent discrimination for prediction of AF after a stroke. However, reports are limited by a high risk of bias, a low number of events in study cohorts, and a lack of impact studies. The integration of prediction models into clinical practice for identifying high-risk patients for extended cardiac monitoring after stroke requires prospective assessment before being recommended in guidelines.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2025.01.026.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Data Sharing: Data are available on reasonable request. Technical appendix, statistical code, and data set are available from the corresponding author at anna.helbitz@gmail.com.

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