3-9-2021

Utility of the CHA2DS2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis

Tariq Jamal Siddiqi

Muhammad Shariq Usman

Izza Shahid

Jawad Ahmed

Safi U Khan

See next page for additional authors

Recommended Citation

Siddiqi TJ, Usman MS, Shahid I, Ahmed J, Khan SU, Ya'qoub L, Rihal CS, and Alkhouli M. Utility of the CHA2DS2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis. Eur J Prev Cardiol 2021.

Authors

Tariq Jamal Siddiqi, Muhammad Shariq Usman, Izza Shahid, Jawad Ahmed, Safi U Khan, Lina Ya'qoub, Charanjit S. Rihal, and Mohamad Alkhouli

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwab018

FULL RESEARCH PAPER
Risk prediction

Utility of the CHA_2DS_2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis

Tariq Jamal Siddiqi[1†], Muhammad Shariq Usman[1†], Izza Shahid[2], Jawad Ahmed[1], Safi U. Khan[3], Lina Ya'qoub[4] Charanjit S. Rihal[5], and Mohamad Alkhouli[5]*

[1]Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan; [2]Department of Medicine, Ziauddin Medical University, Karachi, Pakistan; [3]Department of Medicine, West Virginia University, Morgantown, WV, USA; [4]Division of Cardiology, Department of Medicine, Henry Ford Hospital, Detroit, MI, USA; and [5]Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Received 8 September 2020; revised 6 January 2021; editorial decision 22 January 2021; accepted 28 January 2021

Aims Anticoagulants are the mainstay treatment for stroke prevention in patients with non-valvular atrial fibrillation (NVAF), and the CHA_2DS_2-VASc score is widely used to guide anticoagulation therapy in this cohort. However, utility of CHA_2DS_2-VASc in NVAF patients is debated, primarily because it is a vascular scoring system, which does not incorporate atrial fibrillation related parameters. Therefore, we conducted a meta-analysis to estimate the discrimination ability of CHA_2DS_2-VASc in predicting ischaemic stroke overall, and in subgroups of patients with or without NVAF.

Methods and results PubMed and Embase databases were searched till June 2020 for published articles that assessed the discrimination ability of CHA_2DS_2-VASc, as measured by C-statistics, during mid-term (2–5 years) and long-term (>5 years) follow-up. Summary estimates were reported as random effects C-statistics with 95% confidence intervals (CIs). Seventeen articles were included in the analysis. Nine studies ($n = 453\,747$ patients) reported the discrimination ability of CHA_2DS_2-VASc in NVAF patients, and 10 studies ($n = 138\,262$ patients) in patients without NVAF. During mid-term follow-up, CHA_2DS_2-VASc predicted stroke with modest discrimination in the overall cohort [0.67 (0.65–0.69)], with similar discrimination ability in patients with NVAF [0.65 (0.63–0.68)] and in those without NVAF [0.69 (0.68–0.71)] (*P*-interaction = 0.08). Similarly, at long-term follow-up, CHA_2DS_2-VASc had modest discrimination [0.66 (0.63–0.69)], which was consistent among patients with NVAF [0.63 (0.54–0.71)] and those without NVAF [0.67 (0.64–0.70)] (*P*-interaction = 0.39).

Conclusion This meta-analysis suggests that the discrimination power of the CHA_2DS_2-VASc score in predicting ischaemic stroke is modest, and is similar in the presence or absence of NVAF. More accurate stroke prediction models are thus needed for the NVAF population.

Keywords Risk prediction • Risk model • CHA_2DS_2VASc • Stroke • Atrial fibrillation

Introduction

European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of CHA_2DS_2-VASc score to predict the risk of ischaemic stroke and subsequently guide oral anticoagulation use in patients with non-valvular atrial fibrillation (NVAF).[1–3] However, the CHA_2DS_2-VASc is solely based on clinical risk factors (e.g. age,

* Corresponding author. Tel: +1 507 255 2502, Fax: +1 507 255 2550, Email: Alkhouli.Mohamad@mayo.edu
†The first two authors contributed equally to the study.

hypertension, diabetes, vascular disease) (Supplementary material online, *Table S1*) that are also known to increase the risk of stroke in patients without NVAF.[4,5] In addition, CHA_2DS_2-VASc does not consider key variables that are increasingly shown to impact the risk of ischaemic stroke in the setting of NVAF [duration of AF, left atrium/left atrial appendage (LAA) size, function, and morphology, cardiac biomarkers, and electrographic markers]. Thus, it has been suggested that this model may not be specific for NVAF-related ischaemic stroke, and may be equally predictive in a patient population without AF.[4] In this meta-analysis, we pooled currently available data to estimate the discrimination ability of CHA_2DS_2-VASc in predicting ischaemic stroke among patients with and without NVAF. We hypothesized that if the CHA_2DS_2-VASc score is specifically predictive of NVAF-related ischaemic strokes, its discrimination ability (C-statistic) would be significantly higher in patients with NVAF than in patients without NVAF.

Methods

This study is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.[6] The PubMed and Embase databases were searched from inception up till June 2020 for published articles that assessed the prognostic value of the CHA_2DS_2-VASc score. A detailed search strategy for each database is provided in Supplementary material online, *Table S2*. Other data sources including bibliographies of relevant articles and proceedings of scientific meetings. No language or time restrictions were set. All the articles were imported into EndNote X9 (Clarivate Analytics, Thomson Reuters Corporation) and duplicates were removed. Articles were initially screened based on title and abstracts, after which full texts were evaluated.

Studies were included if they (i) used the CHA_2DS_2-VASc score to predict mid-term (2–5 years) and/or long-term (>5 years) risk of ischaemic stroke; (ii) reported the C-statistic (also known as area under the curve or AUC) as a measure of discrimination. Abstracts and unpublished studies were excluded. Included studies were divided into two groups based on whether they included patients with or without AF at baseline. Studies were excluded if they comprised of a mixed population of patients with and without NVAF or if they evaluated the risk of thromboembolic events other than ischaemic stroke. Studies with follow-up of <2 years were also excluded as only a few studies reported data at <2-year follow-up (five NVAF; two without AF), and the authors were of consensus that a follow-up of <2 years had limited predictive value. The following data were extracted: study characteristics, baseline characteristics of patients, and C-statistic [with their corresponding 95% confidence intervals (CIs) or standard errors (SEs)]. The search and data extraction were carried out independently by two reviewers (I.S. and J.A.), and a third reviewer (M.S.U.) was consulted in case of discrepancies. Data extraction was conducted in accordance to the CHARM (Critical Appraisal and Data Extraction for Systematic Reviews of the Prediction Modelling Studies) checklist.[7] The data underlying this article are available in the article and in its Supplementary material online.

Discrimination (measured using the C-statistic) is defined as an assessment of the ability of a risk prediction model to differentiate between subjects who will develop an outcome (in this case, stroke) when compared with those who will not.[8] C-statistic values range from 1.0 (perfect agreement between model-estimated risk and observed events) to 0.5 (random concordance). We defined the discrimination ability of the model based on recent publication as (i) 0.81–0.90 = good discrimination; (ii) 0.71–0.80 = fair discrimination; (iii) 0.61–0.70 = modest/poor discrimination; and (iv) 0.50–0.60 = very poor/almost no association.[9] Review Manager (Version 5.5; Cochrane Collaboration, Oxford, UK) and STATA (v.11; TX, USA) were used to perform the statistical analysis. The generic inverse variance weighted random effects method was used for pooling C-statistic and corresponding SEs from each study. We used random effects model to account for any potential statistical heterogeneity.[10] When SEs were not available, they were calculated from the confidence intervals. The χ^2 test and associated *P*-interaction value were used to test for any statistically significant differences between the NVAF and no NVAF subgroups. Given that the CHA_2DS_2-VASc score is generally used to predict the risk of stroke prior to anticoagulation therapy, we conducted a sensitivity analysis using only studies in which none of the patients received anticoagulation. The refined Prediction model Risk of Bias Assessment Tool (PROBAST) was used to assess the risk of bias in the included studies.[11] The Begg's test was performed to evaluate publication bias in our study. A *P*-value <0.05 was considered significant in all cases.

Results

Of 4469 articles, a total of 17 studies met selection criteria for meta-analysis (*Figure 1*). Studies excluded during full-text review and reasons for their exclusion are presented in Supplementary material online, *Table S3*. Of the included studies, 9 studies ($n = 453\ 747$ patients) reported discrimination ability in NVAF patients, and 10 studies ($n = 138\ 262$ patients) reported discrimination ability in patients without NVAF. The study characteristics are presented in Supplementary material online, *Tables S4* and *S5*. Application of the PROBAST scale demonstrated that the large majority of studies included in this meta-analysis were at minimal risk of bias and had low concern regarding applicability (Supplementary material online, *Table S6*). Begg's test demonstrated no significant publication bias in the included studies (Supplementary material online, *Table S7*).

Discriminatory power of CHA2DS2-VASc at mid-term follow-up (2–5 years)

Meta-analysis of 12 studies [7 NVAF studies ($n = 446\ 274$ patients); 5 studies without NVAF ($n = 108\ 598$ patients)] at mid-term follow-up revealed that the CHA_2DS_2-VASc model had limited discriminatory-power to predict ischaemic stroke [summary estimate: 0.67 (0.65–0.69)] (*Figure 2*). Upon subgroup analysis, this finding was consistent in patients with NVAF [0.65 (0.63–0.68)] and among those without NVAF [0.69 (0.68–0.71)] (*P*-interaction = 0.08).

Discriminatory power of CHA2DS2-VASc at long-term follow-up (>5 years)

Similarly, meta-analysis of seven studies [two NVAF studies ($n = 7473$ patients); five studies without NVAF ($n = 29\ 664$ patients)] at long-term follow-up revealed modest discriminatory power of CHA_2DS_2-VASc to predict ischaemic stroke [summary estimate: 0.66 (0.63–0.69)] (*Figure 3*). This effect was also consistent among NVAF patients [0.63 (0.54–0.71)] and among those without NVAF [0.67 (0.64–0.70)] (*P*-interaction = 0.39).

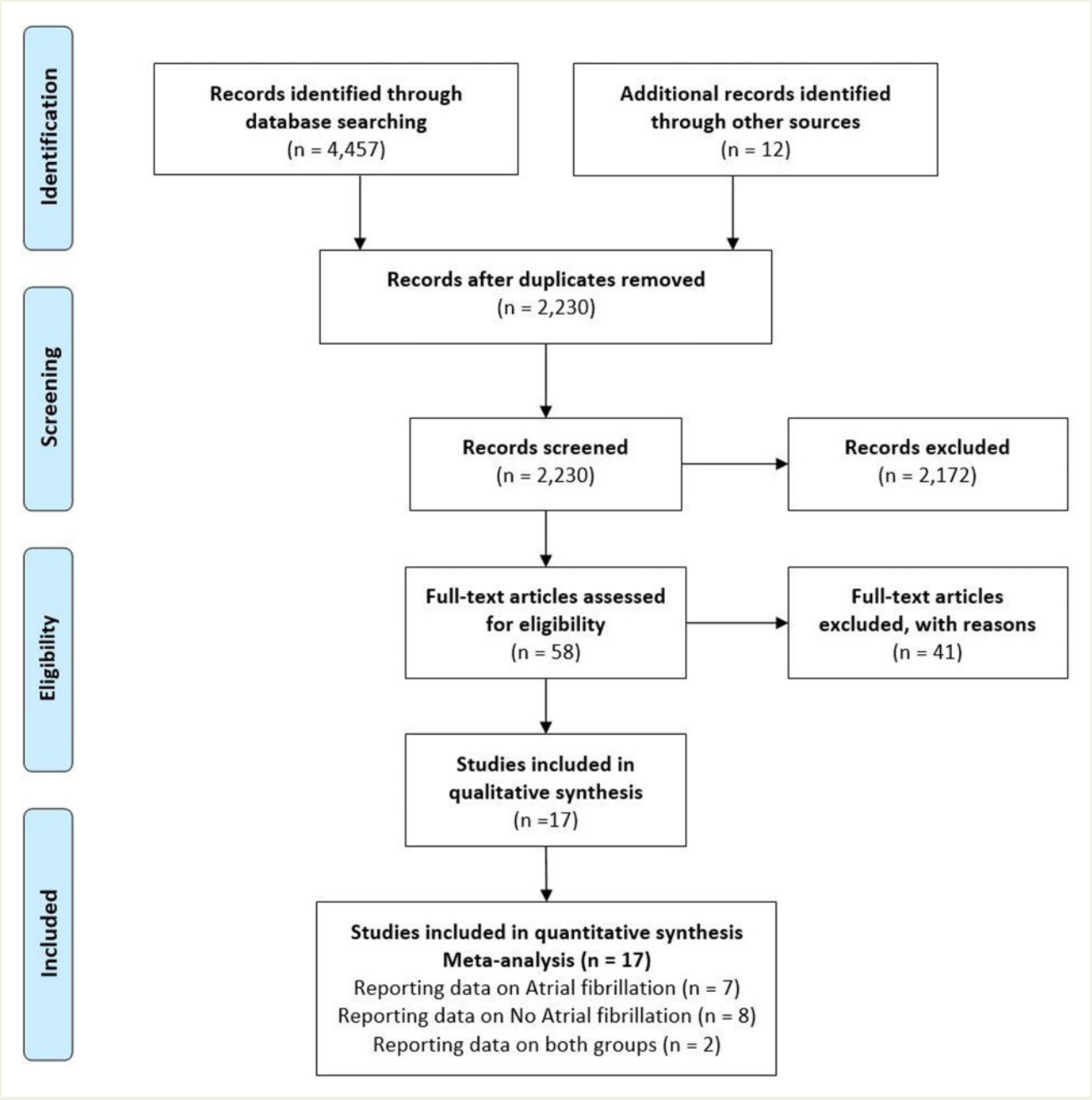

Figure 1 PRISMA flow diagram of the included studies.

Sensitivity analysis to exclusively study patients who did not receive anticoagulation during the study period

Three studies included in our mid-term analysis did not report excluding patients receiving warfarin from their analysis.[12–14] Upon removal of these studies, the results remained similar. Our sensitivity analysis included 473 832 patients ($n = 436\ 547$ NVAF patients; $n = 37\ 285$ without NVAF patients). The overall discrimination was modest (summary estimate: 0.69 [0.67–0.70]). Similarly, both the NVAF (0.68 [0.67–0.70]) and without NVAF (0.68 [0.67–0.69]) subgroups still had modest discrimination, with no significant difference between the two groups (P-interaction = 0.30).

Sensitivity analysis at long-term follow-up was not possible as majority of the studies with >5-year follow-up did not describe how data of patients receiving warfarin were handled during analysis.

Discussion

Assessment of ischaemic stroke risk has become a central element in the management of NVAF. Although many risk schemes have been proposed, tested, and validated in external cohorts, the CHA_2DS_2-

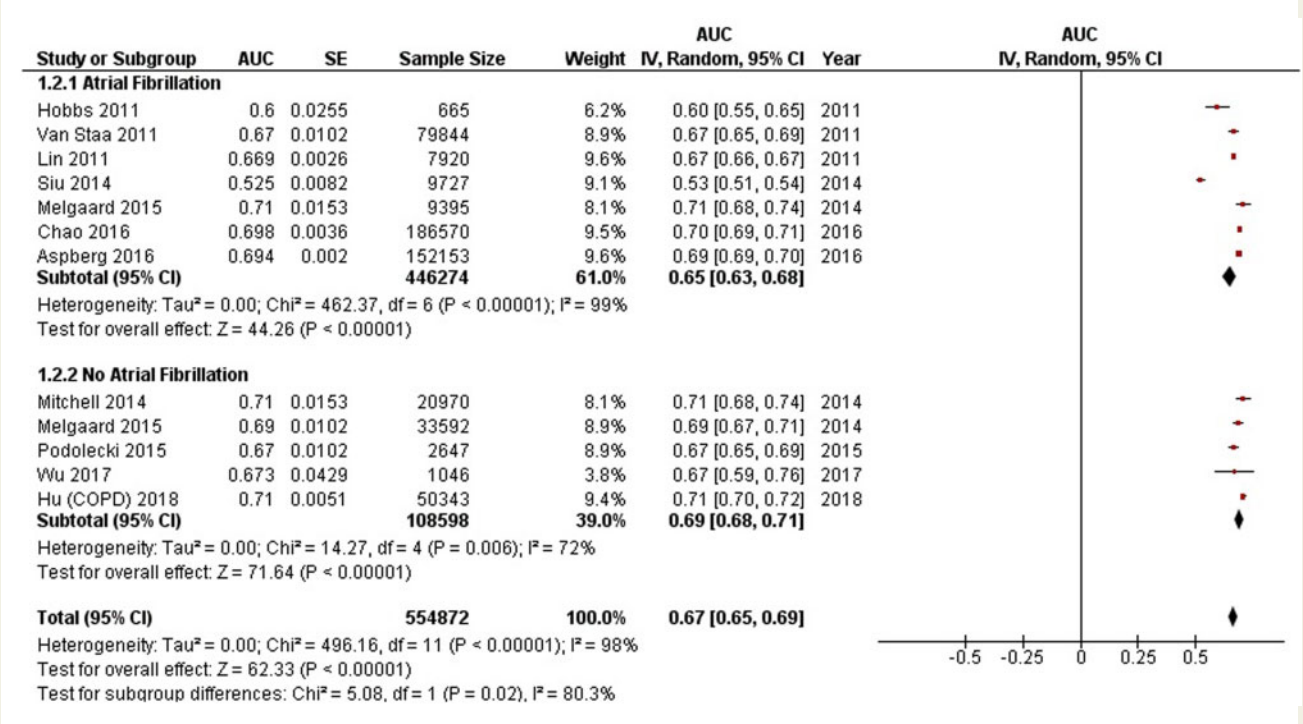

Figure 2 Discriminatory power of CHA_2DS_2-VASc at mid-term follow-up (2–5 years). AUC, area under the curve; CI, confidence interval; SE, standard error.

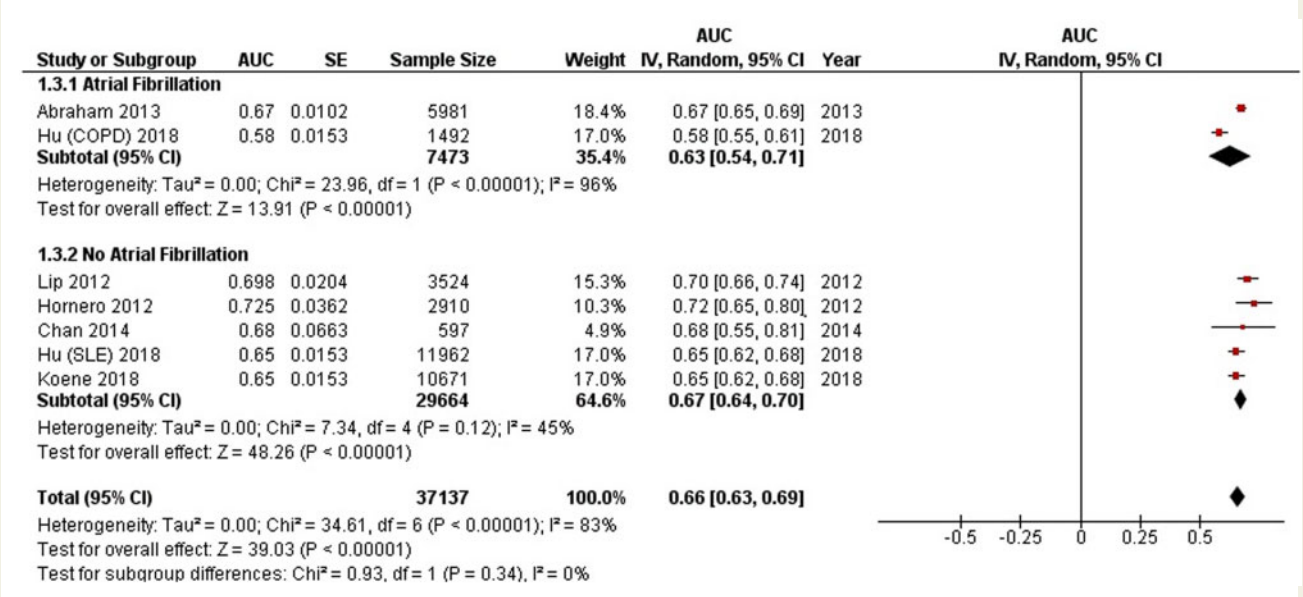

Figure 3 Discriminatory power of CHA_2DS_2-VASc at long-term follow-up (>5 years). AUC, area under the curve; CI, confidence interval; SE, standard error.

VASc score remains the most common risk model used worldwide likely due to its availability and simplicity.[4,16] Indeed, the CHA_2DS_2-VASc score has become increasingly popular in recent years as a useful risk stratification tool for various outcomes and in a variety of clinical settings.[4,17–20] In addition to AF, the CHA_2DS_2-VASc score has recently been observed as a useful predictor for determining adverse outcomes, such as mortality, risk of stroke, major adverse cardiocerebral vascular events, and thromboembolic events in high-risk

patient cohorts, such as those with acute myocardial infarction, chronic obstructive lung disease, or heart failure.[13,20] However, at the same time, concerns have been raised about the specificity of the CHA_2DS_2-VASc in predicting NVAF-related stroke considering: (i) the growing literature on the utility of the CHA_2DS_2-VASc score to predict ischaemic stroke in the absence of NVAF,[4,13,21] and (ii) the fact that this score neither accounts for several key NVAF-specific factors that are known to impact the risk of ischaemic stroke, such as the burden of AF, the size and function of the left atrium (LA) and LAA, nor does it consider the presence of competing risk factors such as complex aortic plaque or carotid stenosis which is associated with double the risk of stroke in patients with NVAF.[4,21] We hence hypothesized that if the CHA_2DS_2-VASc score is a powerful tool in predicting ischaemic stroke related to NVAF, its discriminative power (C-statistic) would be much higher in patients with NVAF vs. those without NVAF.

Our current meta-analysis including ~600 000 patients revealed that the discrimination ability of the CHA_2DS_2-VASc risk score was not different among patients with or without NVAF, suggesting that this risk score might not be specific for the prediction of NVAF-related stroke. Our findings raise an important question: does NVAF have an independent impact on stroke risk, or does the risk of stroke stem from the common vascular risk factors and structural cardiac and vascular abnormalities that accompany NVAF? Although the association between anticoagulation and reduction of the incidence of ischaemic stroke in patients with NVAF is firmly established, the underlying mechanistic basis of stroke in patients with NVAF is complex and considering it as an independent and sole cause of stroke has therefore been challenged.[22] For instance, several studies have shown that the increased risk of ischaemic stroke among patients with left atrial abnormalities (compared with patients with normal left atria) persists after adjusting for the presence of NVAF.[22–25] In addition, if NVAF was the sole cause of stroke, restoration of sinus rhythm would have reduced the risk of ischaemic stroke and mitigated the need for lifelong anticoagulation.[22,26] Nonetheless, a large number of studies have documented a persistent risk of stroke despite maintenance of sinus rhythm for several years after drug-, catheter-, or surgical-rhythm restoration.[26] Thus, the current guidelines recommend continuation of anticoagulation after restoration of sinus rhythm due to the large body of evidence. Indeed, these observations formed the basis of the 'atrial cardiopathy' concept, which suggests that NVAF may be merely a manifestation of a global process that increases the risk of stroke rather than an independent entity.

The modest C statistics shown in our analysis are in-agreement with a large prior meta-analysis that documented a modest performance of CHA_2DS_2-VASc in predicting risk of stroke in patients with NVAF.[27] Although other studies have documented a higher C-statistic for the CHA_2DS_2-VASc score, those studies combined stroke and transient ischaemic attacks, and were more prone to the limitations associated with ascertainment of transient ischaemic attacks.[28–30] Indeed, the original study that led to the wide spread adoption of the CHA_2DS_2-VASc score as a key risk stratification tool in patients with NVAF showed poor discrimination power of the score (C-statistic = 0.61).[31]

Our findings have important implications. The CHA_2DS_2-VASc score is used not only to assess the need for stroke-preventive therapy, but also the type of therapy required.[32] For example, in practice, left atrial appendage closure (LAAC) is mostly conducted on patients with a relatively high CHA_2DS_2-VASc score and a contraindication to oral anticoagulation.[33] Studies from single-arm registries of LAAC often claim benefit of the procedure based on lower observed rates of stroke compared with the rate predicted by CHA_2DS_2-VASc or a similar score.[34–37] This comparison is clearly problematic given that the CHA_2DS_2-VASc score relates poorly to incidence of stroke, as demonstrated by our study. Thus, more accurate risk assessment tools are required for better patient management as well as more reliable research within the AF domain.

Future stroke prediction models should incorporate AF-specific factors such as LA and LAA anatomy and morphology, cardiac biomarkers, and electrographic markers. There is evidence that inclusion of these factors may increase the predictive performance of stroke risk prediction models.[4] For example, it has been documented that each 10 mm increase in LA size increases the risk of stroke by 40–100%,[38] while large and/or less mobile LAA's are associated with up to 6-fold increase in the adjusted risk of stroke.[39] Increase in LA size is also predictive of risk of recurrent cardioembolic or cryptogenic stroke in patients with non-valvular atrial fibrillation (NVAF).[40] Moreover, patients with higher values of troponin-I, troponin-T, and N-terminal pro-B type natriuretic peptide are more susceptible to stroke when compared with those with lower values.[41] Similarly, an abnormal P-wave axis is also associated with higher odds of stroke risk in patients with paroxysmal AF.[42]

The findings of our study further highlight the need for better understanding of the pathological and temporal associations between vascular risk factors, NVAF, atrial abnormalities, and ischaemic stroke. In addition, these findings underscore the need for more comprehensive tools to help clinicians predict the risk of ischaemic stroke both in patients with NVAF and those without NVAF.

Limitations

Our meta-analysis has a number of limitations which need to be considered while interpreting its results. First, this is an aggregate-level meta-analysis and does not account for participant level information. Second, some validation studies were excluded from our analysis as relevant data were not reported. Third, some of our results had significant heterogeneity, which may be perceived as an important limitation. However, the high I^2 in our analysis stems from the variability in sample sizes of component studies of this meta-analysis. This is a known observation in high-powered meta-analyses and is not deemed clinically significant, especially if effect sizes of included studies are similar, as in our analysis.[43] Fourth, considering the observational nature of these studies, confirmation of freedom from NVAF in studies assessing stroke risk in the absence of AF may be limited. Fifth, there may have been patients with subclinical AF in studies without NVAF, which could have contributed to some bias. However, the prevalence of subclinical AF ranges from 2% to 10% in the elderly age group, hence we do not expect this to considerably affect our results.[44,45] Sixth, majority studies did not specify patients via types of AF (paroxysmal or non-paroxysmal), however, since the

risk of stroke does not differ between these two patient cohorts, the type of AF likely does not confound the results of our analysis.[46,47] Seventh, since this is an analysis of observational data, residual confounding is a possibility. And lastly, our manuscript shows that the CHA_2DS_2-VASc score has limited positive predictive value. However, this study did not account for negative predictive value of CHA_2DS_2VASc score.

Conclusion

This large meta-analysis suggests that the discrimination ability of CHA_2DS_2-VASc score in predicting ischaemic stroke is not significantly different in the presence or absence of NVAF. These findings highlight the limitations in our current risk stratification models, and the need for deeper understanding of the association between NVAF and ischaemic stroke.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Conflict of interest: none declared.

Data availability

The data underlying this article are available in the article and in its Supplementary material online.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–2104.
3. Alkhouli M, Noseworthy PA, Rihal CS, Holmes DR Jr. Stroke prevention in nonvalvular atrial fibrillation: a stakeholder perspective. *J Am Coll Cardiol* 2018;**71**:2790–2801.
4. Alkhouli M, Friedman PA. Ischemic stroke risk in patients with nonvalvular atrial fibrillation: JACC review topic of the week. *J Am Coll Cardiol* 2019;**74**:3050–3065.
5. Renda G, Ricci F, Patti G, Aung N, Petersen SE, Gallina S, Hamrefors V, Melander O, Sutton R, Engstrom G, Caterina RD, Fedorowski A. CHA2DS2VASc score and adverse outcomes in middle-aged individuals without atrial fibrillation. *Eur J Prev Cardiol* 2019;**26**:1987–1997.
6. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;**162**:777–784.
7. Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, Reitsma JB, Collins GS. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014;**11**:e1001744.Oct
8. Chowdhury MZI, Yeasmin F, Rabi DM, Ronksley PE, Turin TC. Predicting the risk of stroke among patients with type 2 diabetes: a systematic review and meta-analysis of C-statistics. *BMJ Open* 2019;**9**:e025579.
9. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, McGinn T, Guyatt G. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. *JAMA* 2017;**318**:1377–1384.
10. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009;**172**:137–159.
11. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S; for the PROBAST Group. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. *Ann Intern Med* 2019;**170**:51–58.
12. Siu CW, Lip GY, Lam KF, Tse HF. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm* 2014;**11**:1401–1408.
13. Hu WS, Lin CL. CHA2DS2-VASc score for ischaemic stroke risk stratification in patients with chronic obstructive pulmonary disease with and without atrial fibrillation: a nationwide cohort study. *Europace* 2018;**20**:575–581.
14. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, Wilton SB. Prediction of stroke or TIA in patients without atrial fibrillation using CHADS2 and CHA2DS2-VASc scores. *Heart* 2014;**100**:1524–1530.
15. Proietti M, Farcomeni A, Romiti GF, Di Rocco A, Placentino F, Diemberger I, Lip GY, Boriani G. Association between clinical risk scores and mortality in atrial fibrillation: systematic review and network meta-regression of 669,000 patients. *Eur J Prev Cardiol* 2020;**27**:633–644.
16. Hu WS, Lin CL. Use of CHA2DS2-VASc score to predict new-onset atrial fibrillation in chronic obstructive pulmonary disease patients-large-scale longitudinal study. *Circ J* 2017;**81**:1792–1797.
17. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;**314**:1030–1038.
18. D'Souza M, Carlson N, Fosbøl E, Lamberts M, Smedegaard L, Nielsen D, Torp-Pedersen C, Gislason G, Schou MC. VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. *Eur J Prev Cardiol* 2018;**25**:651–658.
19. Mazzone C, Cioffi G, Carriere C, Barbati G, Faganello G, Russo G, Cherubini A, Sinagra G, Zeriali N, Di Lenarda A. Predictive role of CHA2DS2-VASc score for cardiovascular events and death in patients with arterial hypertension and stable sinus rhythm. *Eur J Prev Cardiol* 2017;**24**:1584–1593.
20. Li C-Y, Chang C-J, Chung W-J, Lin C-J, Hsueh S-K, Lee C-H, Wu C-J, Tsai T-H, Cheng C-I. Assessment of CHA2DS2-VASc score for predicting cardiovascular and cerebrovascular outcomes in acute myocardial infarction patients. *Medicine* 2018;**97**:e11230.
21. Lehtola H, Airaksinen KEJ, Hartikainen P, Hartikainen JEK, Palomäki A, Nuotio I, Ylitalo A, Kiviniemi T, Mustonen P. Stroke recurrence in patients with atrial fibrillation: concomitant carotid artery stenosis doubles the risk. *Eur J Neurol* 2017;**24**:719–725.
22. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke* 2016;**47**:895–900.
23. Kamel H, Hunter M, Moon YP, Yaghi S, Cheung K, Di Tullio MR, Okin PM, Sacco RL, Soliman EZ, Elkind MS. Electrocardiographic left atrial abnormality and risk of stroke: Northern Manhattan Study. *Stroke* 2015;**46**:3208–3212.
24. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Ann Neurol* 2015;**78**:670–678.
25. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S, Okin PM. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. *Stroke* 2014;**45**:2786–2788.
26. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosinski AS, McBroom AJ, Sanders GD. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* 2014;**160**:760–773.
27. Chen JY, Zhang AD, Lu HY, Guo J, Wang FF, Li ZC. CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. *J Geriatric Cardiol* 2013;**10**:258–266.
28. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;**342**:d124.
29. Poli D, Lip GY, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a "real-world" elderly anticoagulated atrial fibrillation population. *J Cardiovasc Electrophysiol* 2011;**22**:25–30.
30. Guo Y, Apostolakis S, Blann AD, Wang H, Zhao X, Zhang Y, Zhang D, Ma J, Wang Y, Lip GY. Validation of contemporary stroke and bleeding risk

stratification scores in non-anticoagulated Chinese patients with atrial fibrillation. *Int J Cardiol* 2013;**168**:904–909.
31. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263–272.
32. Wilhelm M. How to best prevent cardioembolic stroke? *Eur J Prev Cardiol* 2019; **26**:961–963.
33. Asmarats L, Rodés-Cabau J. Percutaneous left atrial appendage closure. *Circ Cardiovasc Interv* 2017;**10**:e005359.
34. López Mínguez JR, Nogales Asensio JM, Gragera JE, Costa M, Cruz González I, Gimeno de Carlos F, Fernández Díaz JA, Martín Yuste V, Moreno González R, Domínguez-Franco A, Benedicto Buendía A, Herrero Garibi J, Hernández Hernández F, Gama Ribeiro V. Two-year clinical outcome from the Iberian registry patients after left atrial appendage closure. *Heart* 2015;**101**:877–883.
35. Park J-W, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, Lopez-Minquez JR, Meerkin D, Valdés M, Ormerod O, Leithäuser B. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv* 2011;**77**:700–706.
36. Saw J, Fahmy P, Azzalini L, Marquis J-F, Hibbert B, Morillo C, Carrizo A, Ibrahim R. Early Canadian multicenter experience with WATCHMAN for percutaneous left atrial appendage closure. *J Cardiovasc Electrophysiol* 2017;**28**:396–401.
37. Korsholm K, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *Eurointervention* 2017;**12**:2075–2082.
38. Benjamin E, D'Agostino R, Belanger A, Wolf P, Levy DT, Framingham H. Study Left atrial size and the risk of stroke and death. *Circulation* 1995;**92**: 835–841.
39. Lee JM, Shim J, Uhm J-S, Kim YJ, Lee H-J, Pak H-N, Lee M-H, Joung B. Impact of increased orifice size and decreased flow velocity of left atrial appendage on stroke in nonvalvular atrial fibrillation. *Am J Cardiol* 2014;**113**:963–969.
40. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, Homma S, Kamel H, Sacco RL, Elkind MS. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. *Stroke* 2015;**46**: 1488–1493.
41. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation* 2012;**125**:1605–1616.
42. Maheshwari A, Norby FL, Roetker NS, Soliman EZ, Koene RJ, Rooney MR, O'Neal WT, Shah AM, Claggett BL, Solomon SD, Alonso A, Gottesman RF, Heckbert SR, Chen LY. Refining prediction of atrial fibrillation–related stroke using the P2-CHA2DS2-VASc score: ARIC and MESA. *Circulation* 2019;**139**: 180–191.
43. Higgins JG. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. The Cochrane Collaboration, 2nd Ed. Chichester, UK, John Wiley & Sons, 2011.
44. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
45. Gherasim L. Subclinical atrial fibrillation, embolic risk, and anticoagulant treatment. *Maedica* 2018;**13**:261–265.
46. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**:183–187.
47. Hohnloser Stefan H, Vamos M. Not all types of atrial fibrillation carry the same stroke risk, but most benefit from oral anticoagulation. *Circ Arrhythm Electrophysiol* 2017;**10**:e004847.