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**EDITORIAL**

# $CHA_2DS_2$-VA instead of $CHA_2DS_2$-VASc for stroke risk stratification in patients with atrial fibrillation: not just a matter of sex

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**This editorial refers to 'Refining the CHA2DS2VASc risk stratification scheme: shall we drop the sex category criterion?' by H. Yoshimura *et al.*, https://doi.org/10.1093/europace/euae280.**

Risk stratification for stroke and systemic embolism is essential in the clinical management of patients with atrial fibrillation (AF). In the past decade, the availability of direct oral anticoagulants (OACs) allowed to provide effective prophylaxis of thromboembolic events in AF patients, with a more favourable risk-benefit profile as compared to warfarin.[1] Among patients with AF, there is a wide variability in the risk of thromboembolic events, ranging from 0.5% per year to 9.3% per year, depending on age, clinical profile, and comorbidities.[1]

The $CHADS_2$ score was the first risk stratification scheme proposed for standard use in patients with so-called 'non-valvular' AF. Introduced in 2001, the score was incorporated into the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines.[2] However, the interpretation of the $CHADS_2$ score should consider that it was validated in a cohort of elderly patients with a high prevalence of heart failure in their medical history. Furthermore, the score was inadequate for identifying truly low-risk patients. Individuals with a $CHADS_2$ score of zero indeed exhibited an annual rate of stroke exceeding 1%, with some studies reporting rates of 2% or more per year.[1,2]

Numerous scores for stroke risk stratification in AF have been proposed over the past 15 years. A dedicated review published in 2022[2] highlighted that a total of 19 risk scores had been reported in literature, accompanied by 327 validation studies and 76 subsequent updates aimed at refining accuracy (primarily related to the $CHADS_2$ and $CHA_2DS_2$-VASc scores). In general, these various risk scores showed largely similar discriminative performance, as evaluated by C-statistics.[2,3] The evaluation of $CHADS_2$ and $CHA_2DS_2$-VASc scores through the C-statistic usually results in a similar performance in predicting stroke and thromboembolism. However, the $CHA_2DS_2$-VASc has the important advantage of identifying patients who are truly at low risk and therefore do not require OACs.[4] The ability of $CHA_2DS_2$-VASc to appropriately identify patients at 'truly low-risk' has been the main reason for the selection of this score as the reference for decision-making on OACs in AF by many, though not all, recent guidelines[5] (*Table 1*).

The current practice of medicine is based on evidence, and consensus guidelines serve to translate available evidence into recommendations, graded by class of recommendation (I, I, or III) and level of evidence (LOE) (A, B, or C).[6] In a systematic analysis of all the available guidelines released by the European Society of Cardiology,[6] it emerged that only a relatively small percentage (16%) of overall recommendations were supported by high-quality evidence, i.e. were supported by randomized controlled trials or systematic reviews and meta-analyses, yielding a LOE A. Similar findings were noted in the guidelines released by other scientific associations. The high prevalence of AF and the severe consequences of stroke require increased efforts to identify patients with AF, even if asymptomatic.[7] There is also a need for user-friendly risk scores to guide appropriate decisions on anticoagulation across a wide range of subjects, including the more frail, multi-morbid and clinically complex patients.[8] There are indeed a substantial variability and heterogeneity in the recommended score for stroke risk stratification, as well as in the class of recommendation and, most importantly, the LOE (*Table 1*).

A detailed analysis of the components of the $CHA_2DS_2$-VASc score identified age and history of prior stroke as the strongest predictors of thromboembolism and stroke in AF patients.[1] Recently, however, there has been some debate regarding the actual value and significance of female sex in this context.[1] A series of studies performed more than 10 years ago highlighted that woman with AF had a higher risk of stroke compared to men, with female sex acting as a 'risk modifier' rather than a risk factor *per se*, with a more pronounced effect in advanced age and in association with additional stroke risk factors.[1] These observations were considered of primary clinical importance, especially in light of the frequent undertreatment with OACs among women, and supported the recommendation for $CHA_2DS_2$-VASc as the reference risk stratification tool in most, but not all, the consensus guidelines (*Table 1*).

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**Table 1** Indications to long-term anticoagulation according to risk scores, with class of recommendation and LOE, according to the guidelines on AF released in the last 6 years

| Guideline for clinical management of patients with atrial fibrillation | Score used | Indications to long-term anticoagulation according to score with class of recommendation and LOE |
|---|---|---|
| 2018 National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand | $CHA_2DS_2$-VA | Score ≥ 2: strength of recommendation: strong; quality of evidence: high<br>Score = 1: strength of recommendation: strong; quality of evidence: moderate |
| 2018 CHEST Guideline and Expert Panel Report | $CHA_2DS_2$-VASc | Score ≥ 1 (male) or ≥2 (female): strong recommendation; moderate quality of evidence |
| 2019 American College of Cardiology, American Heart Association, American College of Chest Physicians and Heart Rhythm Society Update of the 2014 Guideline for the Management of Patients With Atrial Fibrillation | $CHA_2DS_2$-VASc | Score ≥ 2 (men) or ≥3 (women): class I recommendation; LOE A<br>Score = 1 (men) or 2 (women): class IIb recommendation; LOE C |
| 2020 Canadian Cardiovascular Society and Canadian Heart Rhythm Society | CHADS-65 | ≥65 years old: strength of recommendation: strong; quality of evidence: moderate<br>Score ≥ 1: strength of recommendation: strong; quality of evidence: moderate |
| 2020 European Society of Cardiology and European Association for Cardio-Thoracic Surgery | $CHA_2DS_2$-VASc | Score ≥ 2 (men) or ≥3 (women): class I recommendation; LOE A<br>Score = 1 (men) or 2 (women): class IIa recommendation; LOE B |
| 2020 Japanese Circulation Society and Japanese Heart Rhythm Society | $CHADS_2$ | Score ≥ 1: class I recommendation; LOE not reported<br>Use of $CHADS_2$: class I recommendation; LOE B<br>Use of $CHA_2DS_2$-VASc and $CHA_2DS_2$-VA: for both class IIa recommendation; LOE B |
| 2021 National Institute for Health and Care Excellence (NICE) | $CHA_2DS_2$-VASc | $CHA_2DS_2$-VASc ≥ 2 is the ideal threshold for indicating the need for anticoagulation since it offers a good combination of high sensitivity (0.92) and adequate specificity (0.23)<br>Men with a $CHA_2DS_2$-VASc score of 1 are at intermediate risk and anticoagulation should also be considered |
| 2021 Asia Pacific Heart Rhythm Society | $CHA_2DS_2$-VASc | Scores ≥ 2 (men) or ≥3 (women); anticoagulation recommended; LOE not reported<br>Score = 1 (men) or 2 (women): anticoagulation should be considered; LOE not reported |
| 2023 American College of Cardiology, American Heart Association, American College of Chest Physicians and Heart Rhythm Society | $CHA_2DS_2$-VASc | Score ≥ 2 (men) or ≥3 (women): class I recommendation; LOE A<br>Score = 1 (men) or 2 (women): class IIa recommendation; LOE A |
| 2024 Chinese Society of Cardiology, Chinese Medical Association, Heart Rhythm Committee of Chinese Society of Biomedical Engineering | $CHA_2DS_2$-VASc-60 | Score ≥ 2 (male) or ≥3 female: class I recommendation; LOE B<br>Score = 1 (male) or =2 (female): class IIa recommendation; LOE B |
| 2024 European Society of Cardiology and European Association for Cardio-Thoracic Surgery | $CHA_2DS_2$-VA | Score ≥ 2: class I recommendation; LOE C<br>Score = 1: class IIa recommendation; LOE C |

LOE, level of evidence.

In the current issue of *EP Europace*, Yoshimura *et al.*[9] report a study based on an electronic health records data set from the UK which included 195 719 patients with AF followed in primary and secondary care between 1998 and 2016. The study population had a mean age of around 76 years, with 49.2% being women, and only 35.4% of patients were treated with OAC. Notably, OAC use was more frequent in men, despite their lower $CHA_2DS_2$-VASc score (mean 3.3 vs. 3.8) as compared to women, mainly related to older age and higher prevalence of heart failure, hypertension, and prior stroke in women. This finding underscores that in women, there is a lower propensity to prescribe OAC in patients at risk, due to a variety of factors, including actual or perceived frailty, as well as a fear for the expected or predicted risk of bleeding complications.[1,10–12] Among the 126 428 patients not treated with OAC, 8742 individuals experienced at least one thromboembolic event over 413 007 patient-years, and this allowed to analyse the discrimination performance for thromboembolic events of both $CHA_2DS_2$-VASc score and $CHA_2DS_2$-VA score. The authors report no differences according to sex in the lower-risk population, but higher stroke rates were observed in women with the higher-risk scores (i.e. $CHA_2DS_2$-VA ≥ 2). However, this finding has limited practical implications, since female sex potentiates the risk in women who already have the indication to OAC. The C-statistics for thromboembolic risk of $CHA_2DS_2$-VA and $CHA_2DS_2$-VASc scores were similar throughout the study period, with values ranging from 0.62 to 0.71.

A key result of this study from UK[9] is that the $CHA_2DS_2$-VA score showed predictive accuracy comparable to $CHA_2DS_2$-VASc score in identifying AF patients who are at 'truly low-risk' of stroke and therefore do not require OAC. This finding is of great importance, as it aligns with the recommendations of the 2024 Guidelines on AF management recently released by the European Society of Cardiology (ESC).[13] The choice to adopt the $CHA_2DS_2$-VA score was made to for simplify the decision-making for thromboprophylaxis since 'the inclusion of gender complicates clinical practice both for healthcare professionals and patients'. The guidelines also added that the use of $CHA_2DS_2$-VASc 'omits individuals who identify as non-binary, transgender, or are undergoing sex hormone therapy'.[13] In these recent ESC guidelines, the shift to $CHA_2DS_2$-VA score as the reference score for decision making has actually important implications for the LOE, since the LOE for recommending OAC in patients with a $CHA_2DS_2$-VA of 2 or more is only C in current 2024 guidelines, compared to A in previous 2020 ESC guidelines (*Table 1*).

The study by Yoshimura *et al.*[9] holds significant and timely value in supporting the implementation of the $CHA_2DS_2$-VA score in daily practice, and the authors deserve commendation for their important work. Their report should be considered alongside other recent studies that highlight a clear trend over the past decade showing a decrease in AF-related stroke for both men and women, coupled with a marked reduction in sex-related risk differences.[14,15] Detailed data from Finland clearly outline that while the $CHA_2DS_2$-VASc score outperformed the $CHA_2DS_2$-VA score in 2007–2008 (when women had a higher risk of stroke compared to men), the difference in stroke prediction between these two scores progressively diminished over time, and in the years 2017–2018, the $CHA_2DS_2$-VA score had a slightly better performance than the $CHA_2DS_2$-VASc.[15] These observations also indicate a net improvement in OAC implementation in AF patients at risk of stroke, a positive finding that according to studies from specific countries (Finland, Denmark, and the UK) is also coupled with a notable reduction in disparities in OAC usage that previously disadvantaged female patients.[1,14,15]

Future observational studies will be needed to properly verify if the simplification in risk stratification for stroke offered by the $CHA_2DS_2$-VA will lead to broader implementation of OAC among the large variety of AF patients at risk, excluding only those at 'truly low-risk patients', and whether this will occur with no discrimination, in line with the goal of ensuring to all the patients equal access to effective and appropriate care.

Guidelines play a central role in modern medical practice,[6] and their application should involve thorough assessments of individual patients and their comorbidities. In daily practice, it is essential to consider each patient's unique clinical circumstances and to monitor their progression over time. This approach is vital for detecting dynamic changes in clinical status and risk factors, particularly in conditions like AF and other chronic diseases.[1,13]

Recent epidemiological studies clearly indicate that the global burden of AF is increasing.[16] Consequently, providing comprehensive care throughout the patient's journey—addressing arrhythmic issues, underlying heart disease, and associated comorbidities—is a primary goal in modern medical practice. This holistic approach aims to improve clinical outcomes and enhance quality of life for patients with AF.

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## Data availability

There are no new data associated with this article.

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