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Female Sex as a Risk Modifier for Stroke Risk in Atrial Fibrillation: Using CHA_2DS_2-VASc versus CHA_2DS_2-VA for Stroke Risk Stratification in Atrial Fibrillation: A Note of Caution

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Abstract

Stroke prevention is a key clinical concern in the management of patients with atrial fibrillation. Oral anticoagulation treatment reduces the risk of disabling stroke, but the treatment increases the risk of bleeding. For decades, the decision to initiate oral anticoagulation has been guided by clinical risk scoring systems such as the $CHADS_2$ and CHA_2DS_2-VASc scores. In this narrative review, we focus on the recent discussion of the "Sc" (Sex Category) criterion in the CHA_2DS_2-VASc score. Epidemiological considerations when assessing stroke rates in cohorts are discussed, and the implications of different methodological approaches are outlined. Next, we review studies investigating the association of the "Sc" criterion on the stroke rates under various approaches. Lastly, we discuss potential consequences of implementing the recently suggested sex-less CHA_2DS_2-VA score, which leaves out female sex from stroke risk assessment in atrial fibrillation.

Keywords
- stroke/prevention
- cardiology
- epidemiological studies

Stroke Risk in Atrial Fibrillation

Stroke prevention is a key clinical concern when patients present with atrial fibrillation (AF), and appropriate risk stratification is needed to balance the benefit of thromboprophylaxis against the risk of bleeding.[1,2] For more than three decades, scientific evidence has accumulated to show that oral anticoagulant treatment effectively reduces the risk of stroke. Importantly, these observations are consistent across broad and heterogeneous populations of AF patients, including subgroups of age, sex, cardiovascular comorbidities, and cancer.[3,4]

Historically, the $CHADS_2$ score was derived to allow for predicting the risk of stroke among patients presenting with AF.[5] However, a significant proportion of the patients were classified as being at "intermediate" risk of stroke for who anticoagulation recommendations were unclear, and therefore less helpful for guiding the clinicians in the dichotomous decision to initiate oral anticoagulant treatment or not. A refinement was later proposed and validated the CHA_2DS_2-VASc score, which had the strength of better classifying patients at "truly low risk," meaning that the score identified a group of patients who were unlikely to benefit from oral anticoagulant treatment. A recent independent Patient-Centered Outcomes Research Institute systematic review suggested that the $CHADS_2$, CHA_2DS_2-VASc, and ABC scores had the best predictive performance for stroke events in terms of c-statistics.[6] Guidelines have gradually changed recommendations on which patients who should receive stroke prevention with oral anticoagulant treatment based on presence of the number of risk factor included in the CHA_2DS_2-VASc score.

The very purpose of the CHA_2DS_2-VASc score is to be sufficiently reductionist, which enables it to be used as a

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checklist in everyday clinical practice. The CHA_2DS_2-VASc score, which includes female sex as a risk component (sex category: female), was formally implemented for clinical stroke risk stratification in European guidelines in 2010, and this score is currently the preferred risk score in most major international guidelines, which recommend (or at least consider) oral anticoagulation to men with a score ≥ 1 and women with a score ≥ 2.[7–10]

Recently, scientific focus has shifted toward the "sex category (Sc)" criterion with the objective to examine at what score level the 1 point off-set should have clinical implications (i.e. treatment recommendations). In fact, the latest Australian guidelines have recently recommended use of a CHA_2DS_2-VA score deliberately leaving out the female sex criterion from the score.[11]

Epidemiological Considerations When Investigating the "Sex Category" Criterion

In the attempt to investigate the risk of stroke in AF with the intention to make inference about preventive strategies, it is essential to construct a cohort free from oral anticoagulant treatment.

Various methodological considerations and epidemiological choices have been shown to affect the assessment of associated stroke risks (or more commonly, stroke rates), including use of a blanking period to avoid very short individual follow-up times,[12] where AF is diagnosed simultaneously with a stroke event; defining at-risk follow-up time free from oral anticoagulant treatment[13]; and source population with careful consideration of factors, such as different ethnic origin, coding practice and validity, and hospital-based cohorts versus primary care-based cohorts, etc.[14–17] Also, methodological issues need scrutiny, especially where observational cohorts were confined to AF patients who were never ever started on oral anticoagulation, thus "conditioning on the future" and biasing toward lower event rates.[18] Similarly, some cohorts report only baseline anticoagulation status, with no assessment of change in anticoagulation use during follow-up anticoagulation.[19] Indeed, censoring for anticoagulation initiation at follow-up is one appropriate methodology for some investigations; the overall message is that anticoagulant treatment as a yes/no adjustment on multivariate analysis is not an adequate approach to account for the effect of oral anticoagulant treatment on stroke risk.[13]

It is well known that individual risk factor components in the CHA_2DS_2-VASc score do not carry equal weights.[20] Also, risk factor prevalence change over time reflecting the dynamic nature of risk rather than being a static "one off" assessment at baseline to predict stroke risk many years later.[21,22] Indeed, clinical risk scores (and the CHA_2DS_2-VASc score is no exception) have only modest predictive value for identifying high-risk patients that sustain events and should not be overinterpreted given they are mere simplifications of assessing risk.

Therefore, investigators may be interested in examining the contribution of individual diseases in terms of stroke risk factor(s) to ascertain whether or not these differ among females and males. Nevertheless, guidelines recommend assessing stroke risk based only on score point levels, regardless of which risk components (age, heart failure, diabetes, etc.) that contribute to the specific score level. While this distinction may seem trivial, it is central when investigating associated stroke risk. Making inference about difference in stroke risk in females versus males with 1 point on the CHA_2DS_2-VA(Sc) score is not equivalent to investigating the difference in stroke rates in females and males with (e.g.) hypertension and no other prevalent risk factors. Similarly, there is an interpretational difference in comparing a female with a score level of 3 with a male at same score level, than when comparing a female aged 68 (1 point) with heart failure (1 point) and hypertension (1 point) with a male peer with the exact same risk factor profile. In other words, creating a model including individual components from the score, that is, the disease rather than the score point level does not allow for inference on score level. Essentially, what is performed is an investigation of differences in associated stroke risk according to sex when holding other components (diseases) constant. While this approach has scientific advantages, it also has major limitations regarding the interpretation on how the score functions and translates into use in clinical practice.

Stroke Rate Contribution from the "Sex Category" Criterion

Observations of a higher incidence of stroke in women compared with men in the setting of atrial fibrillation date back also to before the introduction of the CHA_2DS_2-VASc score.[23–25] Women do carry an overall higher risk of thromboembolism, but the sex-specific differences in stroke risk vary across CHA_2DS_2-VASc score levels.[26]

However, in an analysis of the J-RHYTHM Registry, an excess risk in females versus males was not observed.[27] Notwithstanding that this registry cohort consisted of a selected proportion of AF patients opting in for the study (and therefore may have limited generalizability), the methodological approach to reach their conclusion may be questioned. Although some data were presented as rates, it appears that the data were not time to event but rather binary outcomes with no information on time per subject. Indeed, the relative measure provided was odds ratio (OR), thus hampering comparison with other studies in this field, which traditionally have used longitudinal data with information on at-risk time to report relative measures based on incidence rates. In the Japanese study, a multivariable logistic regression approach was applied to reach the conclusion that female sex was not a risk factor for thromboembolism when adjusting for various risk factors and treatment. As mentioned, such an approach may be of scientific interest, but the applicability into clinical practice on stroke risk assessment based on score points in AF is lacking.

In a large Swedish cohort of unselected AF patients, Tomasdottir et al showed that associated stroke rates were different when using a point-based approach than when using a disease-specific risk factors approach stratified

according to sex.[28] They argued that the excess stroke risk observed among females was score level dependent, but this itself does not allow inference on the magnitude of excess risk that female sex contributes within each level of the score.

A large Danish cohort study of nonanticoagulated patients with AF reported overall higher risks of stroke in women, but when stratified by CHA_2DS_2-VASc score levels, the higher risk for females was only evident among those with CHA_2DS_2-VASc scores ≥ 2.[29] What this study added was the specific contribution from the "Sc" criterion as a difference per stratified score level. This allowed for inference on the magnitude of the risk-differences due to sex across score levels (i.e. effect modification). The risk ratios from the model including the interaction term between sex (males as reference) and score level showed that females were consistently at higher risk of stroke at score levels at 1 or higher (►**Fig. 1**).

Potential Clinical Consequences of Changing the Risk Score

Some studies support the existence of a sex-specific stroke risk variation according to CHA_2DS_2-VASc score levels.[28,30] These observations have led to the implementation of the CHA_2DS_2-VA score as the preferred stroke risk score for guiding anticoagulation decisions in patients with AF in the recent guidelines from Australia and New Zealand,[31] despite the lack of any comparative formal risk score validation. Although tempting, the maneuvre of completely ignoring the well-established sex-differences in stroke risk may have deleterious consequences.[32]

First, an overall underuse of oral anticoagulation across all levels of the CHA_2DS_2-VASc score has been repeatedly reported, the reasons for which are not entirely understood.[33,34] Second, women do carry an overall higher risk of stroke than their male counterparts, and thus the greatest benefit in terms of absolute stroke risk reduction is among women. Several reports of sex-differences in oral anticoagulation use have indicated that underuse and nonadherence is most frequent among women.

A comprehensive report from 2017 based on the American PINNACLE National Cardiovascular Data Registry demonstrated that women were less likely than men to receive oral anticoagulation across all CHA_2DS_2-VASc score levels.[35] According to guidelines, female sex is not associated with bleeding once oral anticoagulation is initiated; therefore, reluctance to prescribe anticoagulation due to bleeding risk is an unlikely explanation for this consistent pattern of underuse.[10] More recently, a Tasmanian report also demonstrated a higher degree of the underuse of oral anticoagulation among women than men with AF and a guideline-recommended indication for oral anticoagulation, with an adjusted OR of 0.83 (95% confidence interval [CI]: 0.69–0.99).[36] Another sizeable contemporary American report using Medicare data found female sex to be a negative predictor of initiation of oral anticoagulation in AF with an OR of 0.59 (95% CI: 0.55–0.64).[37]

Once anticoagulation is prescribed, adherence, and persistence to treatment is fundamental for optimal stroke prevention.[38,39] A Dutch study recently found that 34% of patients with newly diagnosed AF had stopped treatment with nonvitamin K antagonists after one year, with female sex being associated with a higher risk of nonadherence.[40]

In summary, women are more likely than men to receive suboptimal anticoagulation, a difference not likely to be explained be differences in bleeding risk profiles. If the Sc

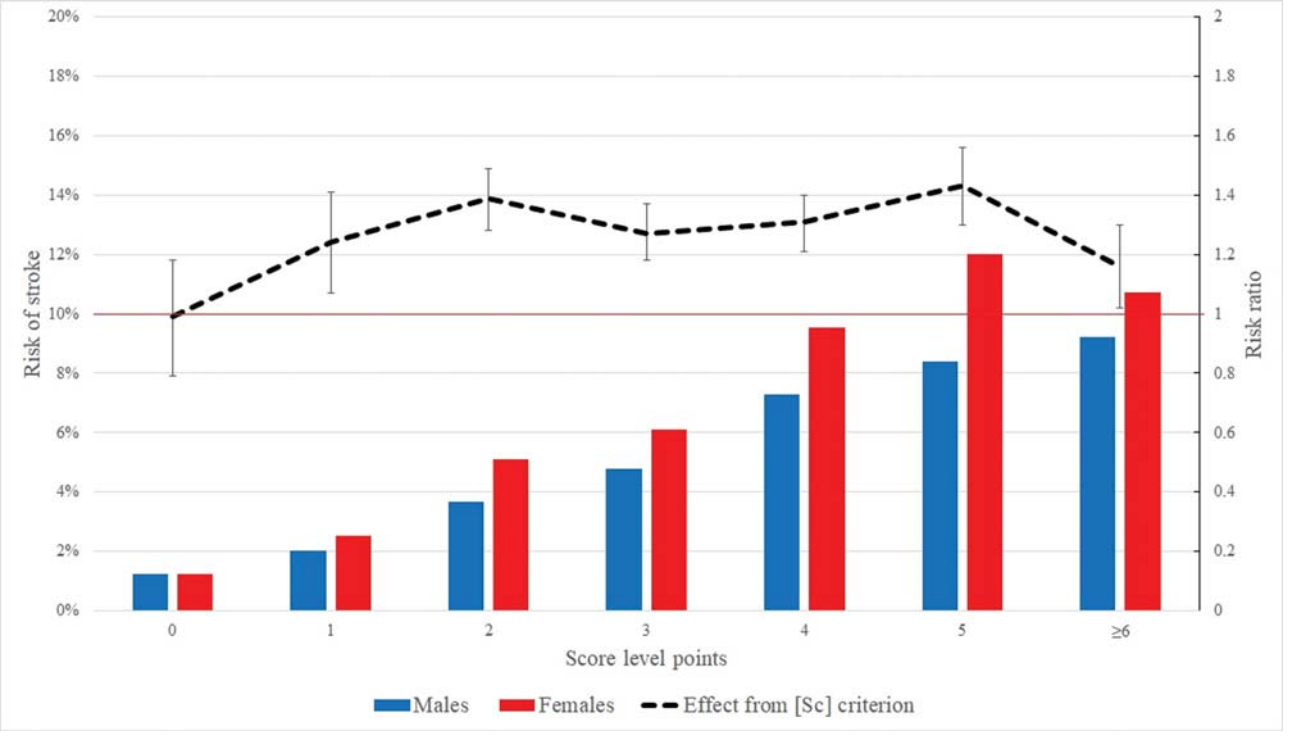

Fig. 1 Graph illustrating the risk of thromboembolism for each score level point for males and females. The dotted line reflects the contribution from the (sex category) criterion as an interaction term. Reproduced from Nielsen et al.[29]

(sex category) component is removed from the CHA_2DS_2-VASc score, we take away the possibility that patients and their treating physicians can weigh in the patient's sex when balancing the expected benefits and harms from oral anticoagulation.[41] Ultimately, this could worsen the established pattern of treatment underuse in women with AF. Future studies may confirm that there are valid reasons causing that women receive oral anticoagulation less frequently than men, but until such data exist, a continued need for focus on sex-differences in stroke risk in AF is preferable.

Conflict of Interest

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