Sex differences in stroke risk have changed: should we reconsider risk stratification?

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Stroke risk stratification in patients with atrial fibrillation (AF) is a central component in the management of the disease and for determining the need for oral anti-coagulant (OAC) treatment. Current guidelines recommend using the CHA_2DS_2-VASc score, where female sex counts as one point only if there is at least one additional stroke risk factor.[1] Overall stroke rates have been declining in recent years, and AF management has evolved towards a holistic approach.[2,3] This may potentially have led to a shift in reducing sex differences in AF-related stroke burden. While older studies consistently showed that females with AF are at higher stroke risk than males,[4] contemporary data are lacking to determine if female sex should still be considered a stroke risk modifier in AF risk scores and guidelines.[5,6]

In this issue of The Lancet Regional Health–Europe, Teppo et al. evaluated the predictive performance of the CHA_2DS_2-VASc score versus a modified version, the CHA_2DS_2-VA score, i.e. leaving out the sex category component of the original score.[7] The evaluation factored temporal trends into the analytic approach to account for the overall attenuation of declining stroke rates. Using data from the FinACAF Study, a total of 144,879 patients with new-onset AF and free from OAC treatment was identified from 2007 to 2018. During 1-year follow-up, 2.7% experienced an ischemic stroke, with the highest stroke rates among patients included in the years 2007–'08 and a CHA_2DS_2-VASc score of 7 points (event rate of 28.2/100 person-years). Interestingly, the study finds that in earliest years, the CHA_2DS_2-VASc score performs as well or better than CHA_2DS_2-VA in predicting stroke risk. However, this trend reverses over time, and by 2017–2018 CHA_2DS_2-VA in most cases performs best. Although the overall differences are marginal, the study suggests that CHA_2DS_2-VA might be more suitable in more recent years.

More recent data needs to be evaluated to further confirm that the trends continue beyond 2018. In our recently published study examining time trends for sex differences in stroke risk during the period 1997–2020, we observe a similar trend with lowest stroke rates between 2017 and 2020 and with an adjusted relative risk of stroke for women versus men of 1.05 (95% CI 0.86–1.25).[8]

Given the overall relatively poor predictive performance of stroke risk scores, other risk stratification approaches should not be ruled out. Traditional risk scores do not fully capture the nuances of individual patient needs, which may lead to potential under- or overestimation of individual risks because of arbitrary categorization of patients as 'low or high' stroke risk. Indeed, risk stratification should focus on a holistic treatment strategy and not be confined to a single outcome. Such a strategy could encompass not just stroke prevention but also other significant outcomes such as heart failure, vascular dementia, and overall cardiovascular health. This broader focus aligns with the emerging trends in AF management, which emphasize the importance of addressing multiple aspects of the disease and its comorbidities.[3] A future elegant solution could involve identifying patients at the extremes— those with a very low AF-related outcome burden and those at a very high risk who require more intensive clinical monitoring and aggressive treatment strategies to prevent additional cardiovascular complications. This approach would enable clinicians to tailor treatments more precisely, ensuring that low-risk patients are not subjected to unnecessary medication and its associated side effects, while high-risk patients receive the comprehensive care needed to mitigate their risks.

Additionally, it is crucial to evaluate whether the current variables in the CHA_2DS_2-VASc score are the most optimal or others should be considered to move towards a more personal treatment strategy. Many AF related outcomes are complex diseases with a significant genetic component. For example, ischemic stroke has an estimated heritability of ∼38%,[9] making the genetic factor a highly important risk factor to consider. One way of including genetics in risk stratification models is by combining the effect of the associated genetic variants into a single polygenic risk score. This method is gaining popularity and shows promising predictive performance for ischemic stroke in combination with the CHA_2DS_2-VASc score.[10] However, there are challenges that need to be addressed before a genetic component can be applied in the clinic, such as education of health care professionals and limited

generalizability to non-European populations. Finally, it should be evaluated whether the gain in predictive performance is large enough to justify adding an extra layer of complexity, while appreciating that availability of individual genetic information may be the reality for the future healthcare system.

By leveraging a combination of clinical data, genetic insights, and patient-specific factors and potentially shifting focus towards a broader view of AF-related outcomes, we can advance to a more nuanced and effective risk stratification and management strategies that better serve the diverse needs of patients with AF. Yet, more studies are warranted for uncovering the full potential of including genetic predisposition in risk stratification of AF-related burdens of the disease.

Contributions
The conceptualisation, writing, review, and editing was equally contributed for AK Nøhr and PB Nielsen.

Declaration of Interests
AK Nøhr: None. PB Nielsen: Personal consultant honorarium and lecturing honorarium from Daiichi-Sankyo outside the related work.

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