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## Stroke risk in female patients with atrial fibrillation: Relationship to current guideline recommendations

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### Introduction

Atrial fibrillation (AF) is a major cause of stroke and mortality, and optimal stroke risk stratification is essential to reduce the burden of stroke among AF patients.<sup>1</sup> The increase in AF prevalence has correspondingly increased the proportion of AF patients that should be considered for antithrombotic treatment. Preventing stroke with oral anticoagulant treatment (OAC) comes at the cost of an increased

bleeding risk, but the net clinical benefit of treatment is often substantially higher than withholding treatment.<sup>2</sup>

Risk stratification helps identify those AF patients who may or may not need thromboprophylaxis.<sup>3</sup> In general, the default should be the provision of stroke prevention by means of oral anticoagulation unless patients are low risk.<sup>4</sup> However, 'low risk' categorization is often arbitrary and has been subject for much debate. A source for this debate originates from the interpretation of estimated stroke risk on the basis of the risk factors, which are included in stroke risk stratification tools.<sup>5,6</sup> Here we briefly review the current AF guidelines recommendations on OAC treatment. Specific focus is given to the importance of concise interpretation of female sex as a risk factor for stroke in AF.

### **Guideline discrepancies**

Contemporary European and North American AF guidelines recommend the use of CHA<sub>2</sub>DS<sub>2</sub>-VASc (Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, Sex category) score.<sup>3,7</sup> The maximum cumulative score is 9, where female sex contributes one point to reflect the overall increased risk of stroke among female AF patients. However, the threshold for recommendations are not aligned, where different recommendations of antithrombotic therapy varies across different risk categories, see Table 1.

Currently, North American guidelines for managing AF patients suggest that patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 may be considered for no antithrombotic therapy, aspirin, or oral anticoagulant.<sup>7</sup> In an observational cohort study including 49916 AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 beyond sex, treatment with warfarin in comparison with no treatment or aspirin exhibited a positive net clinical benefit.<sup>2</sup> These data supported the 2012 European Society of Cardiology<sup>8</sup> (ESC) guidelines to

recommend OAC treatment, and also showed that aspirin should not be considered as an effective stroke prevention strategy in these patients. However, the North American guidelines do not separate the risk factor of sex from other (clinical) stroke risk factors. Thus, female patients with no additional stroke risk factors may even be considered for antithrombotic therapy based on these recommendations. To our knowledge, there has not been evidence published to support the use of aspirin treatment to prevent stroke in female patients with AF with no additional stroke risk factors.

In Europe, the guideline recommendations differentiate between males and females by setting different point level thresholds for recommending OAC treatment initiation. In the contemporary ESC AF guidelines, the treating physician is required to make a choice based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score points and an individualized stroke risk assessment.<sup>3</sup> Specifically, for male patients with a single non-sex specific stroke risk factor, i.e. 1 point and females with 2 points, the guideline suggest to ‘*consider*’ OAC treatment initiation. For two or more non-sex specific CHA<sub>2</sub>DS<sub>2</sub>-VASc score risk factors, i.e. male patients with  $\geq 2$  points and females with  $\geq 3$  points, there is a clear recommendation of OAC treatment (Table 1).

Withholding OAC treatment initiating in patients with a score of 2 (i.e. two risk factor components for males, and one risk factor for females) was investigated in a large cohort of AF patients who did not receive antithrombotic treatment.<sup>9</sup> The rate of thromboembolism per 100 person-years was 1.97 – for most clinicians, clearly high enough to warrant stroke prevention. Nevertheless, the approach of recommending treatment based on rates from cumulative score by including sex as a risk factor may be too simplistic.

### **Stroke risk in female AF patients**

Madsen and colleagues recently provided an update on the impact of conventional stroke risk factors on the occurrence of stroke in female individuals compared with males.<sup>10</sup> They accurately highlighted the consistently reported higher crude risk of ischemic stroke among female AF patients compared with males. However, significant interactions between female sex and age or other stroke risk factors have been repeatedly reported.

Indeed, in terms of stroke risk stratification, including female sex (the “Sc” component) as an independent stroke risk factor in AF may be too simplistic to appreciate the higher stroke risk observed among female AF patients, which has a dependency on age and other risk factors. In a recent analysis including nearly 240,000 newly diagnosed AF patients (48.7% females), we investigated the “Sc” component as a prognostic factor rather than a risk factor for stroke within the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>11</sup> This investigation indicated that the excess female sex-related risk of stroke was evident only in the presence of other CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors, especially among female AF patients with  $\geq 2$  concomitant non-gender CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors. Indeed, when including female sex as an interaction term (and not an independent risk factor), we observed a 5-year risk ratio of stroke between 1.16 (95%CI, 1.02 – 1.30) and 1.43 (95%CI, 1.30 – 1.56), dependent on the number of concomitant sex-specific CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors.

These results highlighted that female sex could be considered a *risk modifier* rather than an independent *risk factor* for stroke among AF patients. Hence, female AF patients without other CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors could be considered to be stratified into a ‘low stroke risk’ category, and thus potentially requiring no antithrombotic therapy. This would entail that the initial step in stroke risk stratification is the identification of low risk patients (CHA<sub>2</sub>DS<sub>2</sub>-VASc 0 in males, 1 in females) who do not need any antithrombotic therapy, following which stroke prevention (i.e. oral anticoagulation)

should be offered to those with  $\geq 1$  stroke risk factors.<sup>4</sup> This has also been acknowledged in the recent European Heart Rhythm Association Consensus Document on sex differences in cardiac arrhythmias<sup>14</sup>, which emphasized a consistent underrepresentation of female patients in AF trials and recommended consideration of OAC use in all female patients with one or more additional non-sex specific stroke risk factors (i.e., a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$ ). Nevertheless, OAC treatment remains in general under-used among AF patients with low bleeding risk and high stroke risk, and clearly warrants more insight and efforts among prescribing physicians.<sup>12</sup> Yet, this pattern was consistent among males and females.<sup>13</sup>

Importantly, regular clinical follow-up for the re-assessment of stroke risk factors is mandatory, since the risk is not static and may change over time.<sup>9</sup> Indeed, the dynamic changes in stroke or bleeding risk profile are the best predictors of adverse outcomes.<sup>9,10</sup> While it may seem appropriate to consider a change in the use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score to reflect that male and females have different stroke risk across different score levels, we do not recommend such change at this time. We fear this could even potentially confuse prescribing physicians, unintentionally indicating that women carry excess stroke risk relative to male peers.<sup>11</sup> Accurate stroke risk prediction in AF is important; however, the prediction accuracy should be balanced against the practicality and ease of use in a busy clinical setting. The clinical value of refining stroke risk stratification may therefore lie in improving the identification of patients at sufficiently low risk of stroke. Current data suggests that female AF patients with no additional stroke risk factors are such candidates, and we therefore question the current US guideline options that include aspirin treatment or OAC treatment for these patients.

Ethical Statement

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ACCEPTED MANUSCRIPT

**Table 1:** Contemporary guideline recommendations for initiating antithrombotic treatment in AF patients based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

	North American guideline recommendations		European guideline recommendations	
	Females	Males	Females	Males
CHA <sub>2</sub> DS <sub>2</sub> -VASc = 0	N/A*	No therapy	N/A*	No therapy
CHA <sub>2</sub> DS <sub>2</sub> -VASc = 1	OAC, aspirin, or no therapy		No therapy	Consider OAC
CHA <sub>2</sub> DS <sub>2</sub> -VASc = 2	Recommend OAC		Consider OAC	Recommend OAC
CHA <sub>2</sub> DS <sub>2</sub> -VASc ≥ 3	Recommend OAC			

\*Females cannot score 0, as female sex triggers 1 point