


Sex as a Risk Factor for Atrial Fibrillation-Related Stroke

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Abstract

Keywords

- ▶ atrial fibrillation
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- ▶ stroke
- ▶ oral anticoagulants

Stroke prevention is crucial for the management of patients with atrial fibrillation (AF), and several risk factors have been identified, which increase the risk of AF-related stroke. Among these factors, female sex has been repeatedly associated with AF-related stroke risk; nonetheless, trends toward lower use of oral anticoagulant in women with AF were also reported. In this clinical focus, we discuss about the role of female sex as a risk factor for AF-related stroke, and reflect on the clinical implications of its inclusion among the risk factors for thromboembolic risk stratification in patients with AF.

Atrial fibrillation (AF) increases the risk of stroke and thromboembolism by fivefold, but this risk is not homogeneous, and depends on the presence (or absence) of various risk factors. In the Stroke in AF Working Group systematic review,¹ prior stroke/transient ischemic attack, increasing age, hypertension, and diabetes mellitus were the strongest, most consistent independent risk factors. In patients with AF, female sex was inconsistently associated with stroke risk but was an independent significant predictor of stroke in three studies (range of individual relative risk [RR]: 1.6–1.9).^{2–4} Interestingly, the evidence for either heart failure or coronary artery disease as independently predictive of stroke was inconclusive. More common and validated risk factors have been used to formulate stroke risk scores, and the most commonly used in guidelines are the CHADS₂ score⁵ and, more recently, the CHA₂DS₂-VASc score.⁶ The Cardiac Society of Australia and New Zealand proposed the CHA₂DS₂-VA score, dropping the Sc (female sex) criterion.⁷

Female Sex as a Risk Modifier for AF-Related Stroke

Aside the Stroke in AF Working Group systematic review,¹ various other studies have confirmed excess risk of stroke in females with AF. Wagstaff et al⁸ reported a 1.31 (95% confidence interval [CI]: 1.18–1.46) elevated risk of AF-related stroke in women. A more recent meta-analysis of cohort studies demonstrated a higher risk for women to experience AF-related stroke (RR: 4.05, 95% CI: 2.52–6.50), compared to men (RR: 1.77, 1.40–2.24).⁹ In the ORBIT-AF registry, women had a higher risk of AF-related stroke compared to men (hazard ratio [HR]: 1.39, 95% CI: 1.05–1.84); moreover, women had more symptoms and worse quality of life.¹⁰ Consistently, in a Swedish nationwide cohort, among patients with lone AF (age <65 years and no vascular disease), the annual stroke rate tended to be higher in women than in men, although nonsignificant (0.7 vs. 0.5%, *p* = 0.09); overall, women with AF remained at modestly

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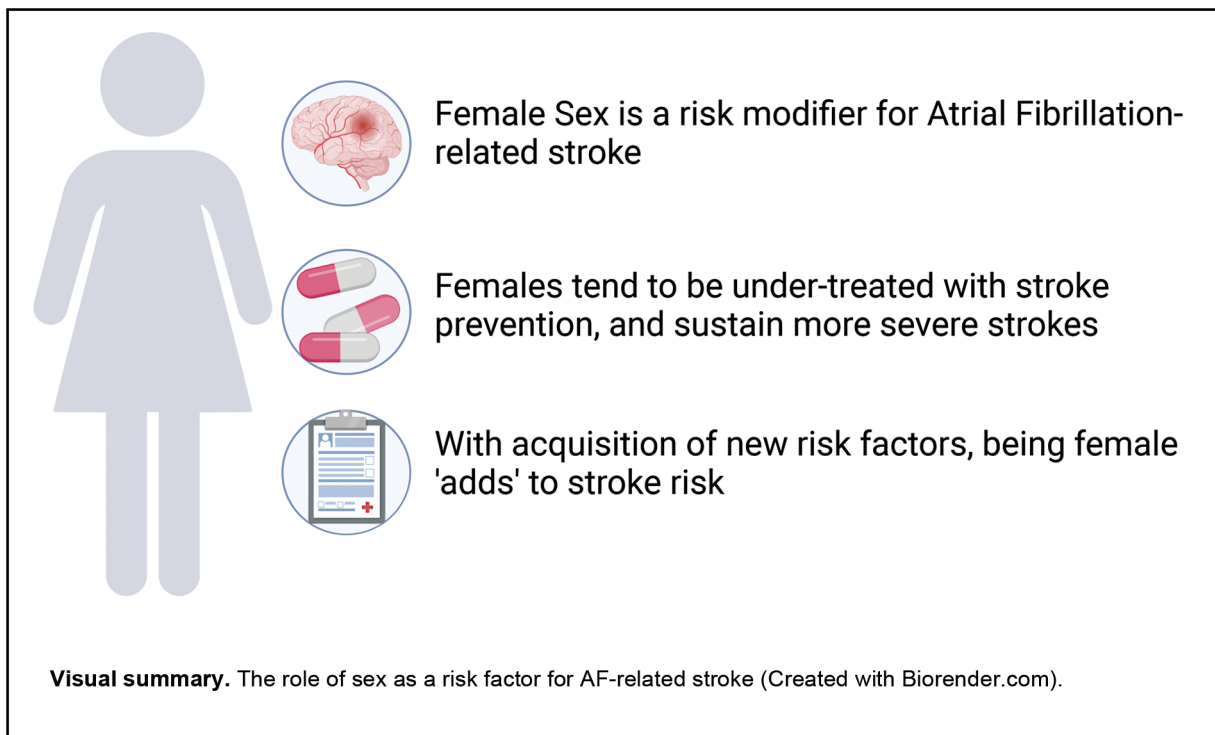
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increased risk of stroke compared to men.¹¹ In the Danish nationwide registries, the risk of thromboembolism for a score point shows an excess of stroke rates in the presence of one additional stroke risk factor amongst females AF patients compared to males.¹² Consistently, Avgil Tsadok et al¹³ reported that females AF patients had an adjusted HR of 1.14 (1.07–1.22) for the risk of stroke events. In another meta-analysis, the risk of stroke was found to be significantly higher in women than in men with AF (HR: 1.24, 95% CI: 1.14–1.36), and at meta-regression analyses this association appeared to be influenced by age and uptake of oral anti-coagulants (OACs).¹⁴

Whether the differential association of AF, death, and cardiovascular disease in women is causal is unclear. Using administrative databases from Ontario, Buhari et al¹⁵ found that female sex was associated with 1.27-fold higher risk of stroke after adjusting for CHA₂DS₂-VASc factors. Nonetheless, females were older, diagnosis of AF was more likely made in the emergency department, often without cardiologist assessment; and following AF diagnosis, females were less likely to have a cardiology visit or to receive stroke prevention therapy.

Differences in OAC Therapy and Outcomes

Buhari et al suggested that older age and inequities in cardiovascular care may partly explain higher stroke rates in females with AF.¹⁵ Other contemporary cohort studies also show sex-related differences in prevalence, treatment, and outcomes, and female AF patients may be disadvantaged.

In an Italian cohort, prevalence of AF was higher in males, but thromboembolic risk was generally greater in females, who less frequently received OAC.¹⁶ Similar results were

observed in the Tasmanian Atrial Fibrillation Study, where female AF patients were less likely to receive guideline-recommended treatment irrespective of CHA₂DS₂-VA scores of 0, 1, or ≥ 2 .¹⁷ The authors discuss that the introduction of CHA₂DS₂-VA stroke risk stratification by the Australian AF guidelines could potentially lead to under-recognition of female sex as a risk factor that may affect stroke risk. Not only that female AF patients tend to be undermedicated with OAC: when they present with a stroke, they also experience more severe strokes, as reported by data from the Austrian Stroke Unit Registry, in which women patients with AF who suffered a stroke showed higher median National Institutes of Health Stroke Scale scores compared to men.¹⁸ Interestingly, the association between sex and stroke severity appeared independent of age, other comorbidities, and previous functional status.¹⁸

CHA₂DS₂-VASc or CHA₂DS₂-VA for Stroke Risk Stratification?

So, the question arises whether female sex should be included into risk scores for assessing stroke risks in patients with AF. It is worth remembering that there are many stroke risk factors and only the more common ones have been included in stroke risk stratification schemes in AF. Importantly, all the stroke risk stratification schemes (and CHA₂DS₂-VASc or CHA₂DS₂-VA are no exception) are, by design, mere simplifications to help decision-making, and are generally reductionist. All risk scores based on clinical factors have similarly modest predictive value for identifying high-risk patients.

Of course, there are more complicated stroke risk scores, some including biomarkers which marginally improve on prediction, at least statistically. Even then, in many of the

derivation and validation studies, their C-indexes are less than 0.7, indicating only modest predictive value. Also, statistical significance is not the same as clinical significance, which need to be balanced with practical application.^{19–21}

The other major limitation is that risk is dynamic and not static. Also, single stroke risk factors do not carry similar risks. Many risk factors are determined at baseline, and the event of interest (i.e., stroke) is determined many years later, while risk changes with ageing and incident comorbidities. One recent study found that approximately half of patients aged under 65 years had an indication for anticoagulation, while the remaining half became eligible for anticoagulation at a rate of 6% per annum, most commonly because of developing comorbidities.²² In Taiwan, 80% of initially low risk AF patients acquired one or more comorbidities, and this new comorbidity occurred approximately 4 to 5 months after the AF diagnosis.²³

Taken together, these data suggest that AF-related stroke risk evaluation should be focused on risk factors and concomitant comorbidities, rather than relying on any artificial categorization into low, moderate, and high-risk strata.

Published Evidence for CHA₂DS₂-VA

What is the published evidence for CHA₂DS₂-VA? In the FU-CREATE claims database, among 9,733 AF patients who had never been prescribed anticoagulant agents (hence, potential conditioning on the future), C-statistics for the CHA₂DS₂-VASc and CHA₂DS₂-VA scores were similar, both being under 0.7.²⁰ Similarly, in the J-RHYTHM registry, the C statistics of the CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VA scores were 0.577, 0.632, and 0.631, respectively.²¹ In this cohort, patients were nonanticoagulated at baseline, but warfarin was initiated in 23%. During the follow-up, there were no data on the quality of anticoagulation control, and modest absolute differences within the C-indexes, all still under 0.7. The largest analysis comes from the Korean nationwide population-based study, where

the predictive abilities of CHA₂DS₂-VASc and CHA₂DS₂-VA were found to be similar (both under 0.7, at 0.671 and 0.668, respectively). CHA₂DS₂-VA was reported to perform better in predicting ischemic stroke in those patients with risk scores of ≥ 2 and in those age ≥ 75 .¹⁹ While they supposedly excluded patients who received any antithrombotic drugs, 22.7% were on aspirin and 68% were taking OAC.¹⁹

Quo Vadis

Given all the many limitations with clinical stroke risk scores, the default really should be offering stroke prevention unless patients are clearly low risk. Stroke prevention means OAC, whether a well-managed warfarin with a good time in therapeutic range, or a non-vitamin K antagonist OAC. This is reflected in recent guidelines for the management of AF.²⁴

Are we getting any better over the years by considering the female sex criterion? In terms of considering European patients (–Table 1), reviewing crude prescribing data for OAC from the EuroHeart Survey,²⁵ the EORP pilot registry,²⁶ EORP-AF long-term registry,²⁷ and the GLORIA-AF Phase III^{28,29} European cohort (which basically reflects time trends between 2005 onwards with regard to prescribing habits in terms of OAC), we observe an overall trend toward less prevalent undertreatment in female patients.

The EuroHeart Survey was based on the CHADS₂ score (i.e., not considering female sex), while subsequent registries were based on CHA₂DS₂-VASc (i.e., considering female sex). In the EuroHeart Survey, when considering one non-sex stroke risk factor, OAC was used in 64.7% of females, less than amongst males (65.4%). In AF patients with ≥ 2 non-sex stroke risk factors, females less frequently received OAC, undertreated, with 63.8% females prescribed OAC, again less than in males (66.1%).

By the time of the EORP-AF registries and the GLORIA-AF registries, the proportions prescribed OAC with one non-sex stroke risk factor amongst females were $>80\%$. In the

Table 1 Are we getting any better over the years by considering the “Sc” criterion?

	EuroHeart Survey 2005	EORP-AF Pilot registry 2013	EORP-AF Long-Term registry 2016	GLORIA-AF Phase III 2016 (Europe)
N	5,193	3,119	11,090	10,304
Overall use of OAC (%)	64.8%	79.7%	85.1%	89.4%
Use of OAC in 1 non-sex risk factor (%)	[Based on CHADS ₂] 65.1%	[Based on CHA ₂ DS ₂ -VASc] 81.7%	[Based on CHA ₂ DS ₂ -VASc] 85.0%	[Based on CHA ₂ DS ₂ -VASc] 85.4%
Males	65.4%	82.0%	86.3%	83.6%
Females	64.7%	81.0%	82.4%	88.5%
Use of OAC in ≥ 2 non-sex risk factors (%)	65.0%	82.5%	87.7%	90.8%
Males	66.1%	84.1%	88.1%	91.0%
Females	63.8%	80.4%	87.0%	90.6%

Abbreviation: OAC, oral anticoagulation.

European cohort of the GLORIA-AF registry, the proportion of females prescribed OAC with one non-sex stroke risk factor was 88.5%, higher than in males (83.6%), hence undertreatment of females was no longer evident. Amongst those with ≥ 2 non-sex stroke risk factors, OAC prescription in GLORIA-AF was $>90\%$ in both males and females.

Conclusion

Stroke prevention is central to the modern management of AF, but all clinical risk scores have limitations and perform similar in identifying the high-risk patients and only very modestly. Stroke risk is also not static, but dynamic in nature.

The fact that remains is that females with AF tend to be undertreated with OAC in many older studies and sustain more severe AF-related strokes. With the acquisition of new risk factors, being female adds to AF-related stroke risk. Hence, rather than a categorical approach to stroke risk stratification and treatment decision making, the initial step should be to identify low-risk patients who do not need any antithrombotic therapy, following which we offer anticoagulants to those with ≥ 1 stroke risk factors. Inclusion of female sex as an AF-related stroke risk modifier draws attention to the risks associated with female AF patients, and over the years, the inclusion of female sex in the CHA₂DS₂-VASc has led to increased OAC uptake in women, in contrast with the previous trend of lower use of OAC amongst female patients with AF.

Conflict of Interest

G.F.R. reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally. M.P. is Italian national leader of the AFFIRMO project on multimorbidity in atrial fibrillation, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 899871. All other authors have nothing to declare.

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