Gender Differences of Thromboembolic Events in Atrial Fibrillation

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Atrial fibrillation (AF) is the most common clinically relevant arrhythmia and increases the risk of thromboembolism and stroke; however, these risks are not the same for women and men. This review examines the evidence and clinical significance of increased thromboembolic risk in women with AF. The balance of results from over 30 recent studies suggests that female gender is an independent stroke risk factor in AF, and the inclusion of female gender in stroke risk stratification models, such as CHA_2DS_2-VASc, has improved risk assessment. Reasons for the increased thrombogenicity in women remain incompletely elucidated, but biological factors including increased hypertension, renal dysfunction, and hyperthyroidism in female patients with AF; cardiovascular remodeling; increased hypercoagulability, and estrogen hormone replacement therapy in women have been proposed. More importantly, gender differences exist in medical management of patients with AF, and compared with men, women have been found to have greater thromboembolic risk when not on anticoagulants, but may benefit from greater risk reduction when systemically anticoagulated. In conclusion, increased clinician awareness of these gender differences may help to improve the management of patients with AF. **(Am J Cardiol 2016;117:1021−1027)**

Atrial fibrillation (AF), the most common clinically relevant arrhythmia, affects 2.7 to 6.1 million Americans, with prevalence projected to double by the year 2050.[1] The prevalence of AF is 3.2% of the population aged ≥20 years and reaches 20% at age 80.[2] Men have a greater risk of developing AF than women by a factor of 1.5 after adjusting for other risk factors.[3] However, the absolute numbers of men and women with AF are roughly equal because of the higher average life expectancy of women.[4,5] Women make up about 60% of the population with AF aged >75, the median age of AF onset.[6]

AF is associated with a fivefold increased risk of stroke[7] and is attributed with at least 50% of strokes occurring in subjects aged 80 years and older.[2] Many risk stratification models have been proposed to quantify the risk of stroke in AF. The inclusion of female gender as an independent risk factor has been the subject of recent examination. AF is more frequently noted in women presenting with stroke than in men.[8] In addition, women have a worse poststroke outcome than men in terms of motor and cognitive function and activities of daily living.[9] AF is an independent stroke predictor of in-hospital mortality for women but is not for men.[10]

Thus, these gender differences are clinically relevant to make accurate estimations of inherent stroke risk in patients with AF. This is important because patients with AF with the highest stroke risk derive the greatest absolute benefit from systemic anticoagulation.[11] As such, clinician awareness of such gender differences becomes useful when a decision regarding anticoagulation is needed and few or no other risk factors exist. Current European Society of Cardiology (ESC) guidelines recommend that no systemic anticoagulation is required for female patients aged <65 years with lone AF (CHA_2DS_2-VASc = 1) because these patients are considered low risk for stroke, which stands in contrast to other subgroups with CHA_2DS_2-VASc = 1. The primary objective of this review is to provide an updated overview of the existing evidence for gender differences in thromboembolic risk and to discuss the clinical importance of such differences.

Methods

The PubMed database was used to review the English language reports addressing gender differences and thromboembolic risk in AF from 1994 to the present. The search used combinations of terms including "atrial fibrillation," "gender OR sex OR female OR women," and "thromboembolism OR stroke." References of retrieved studies were further reviewed in detail for additional relevant studies and reviews.

Studies were selected for inclusion if they published stroke incidence data in men and in women. The number of women, number of total study participants, mean age of men and women, percent incidence of stroke in men and women, and relative risk (RR) for stroke for women were collected from each study when available. Difference in stroke risk was evaluated by examining the reported RR values, and if these were unavailable, by examining the *p*-value for statistically significant differences in stroke rates between men and women.

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Evidence for Gender Differences in Thromboembolic Risk: We compiled over 30 studies published since 1999 that examine gender and thromboembolic risk, including 5 randomized controlled trials (RCTs) and 24 observational studies (Tables 1 and 2). Of these 30 studies, 17 studies reported that female gender is a significant risk factor,[13–16,19,21,22,25,27,31,33–39] 12 studies reported that female gender is not significant,[17,18,20,23,24,26,28–30,32,40,41] and only 1 study reported that male gender is a significant risk factor.[12] Four additional RCTs compared novel oral anticoagulant drugs (NOAC) and warfarin, providing further data on gender differences (Table 3).[42–45] However, 1 RCT[37] and 1 observational study[34] no longer found a significant difference after multivariate analysis. Four studies, all reporting insignificant gender differences, only reported univariate risk estimates associated with female gender.[18,24,29,32]

Although only 13 of the 25 observational studies reported female gender as significant, 2 of the 12 observational studies that reported no significant gender differences had abnormal age distributions, which may have skewed the data. The Elderly Patients followed by Italian Centres for Anticoagulation (EPICA) study only included patients over 80 years old,[13] and a Beijing hospital study reported that the lack of significant gender differences may be because the female patients were younger and had fewer co-morbidities.[19]

The Stroke Prevention in Atrial Fibrillation (SPAF) trials of the 1990s provided early data on gender differences.[38] These studies reported that women with AF have a greater risk of stroke than men (RR 1.6, $p = 0.01$), and this difference in stroke rate was substantially greater in patients aged >75 years. The largest RCT was the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study with a cohort of 13,559 adults with AF.[36] This was the first RCT with enough end points to examine the influence of gender on stroke risk. The study reported that the annual incidence rates of thromboembolism off warfarin were 3.5% for women versus 1.8% for men (RR 1.9, 95% CI 1.6 to 2.4). The difference between the RR of thromboembolism for women versus men for those aged ≤75 years (RR 1.6, 95% CI 1.0 to 2.3) and those aged >75 years (RR 1.8, 95% CI 1.4 to 2.3) was not statistically different.

Gender as an Independent Stroke Risk Factor: Interestingly, the balance of evidence suggests that female gender is an independent thromboembolic risk factor. Several meta-analyses have also found that women appear to have an increased stroke risk compared with their male counterparts. One meta-analysis of 17 studies reported a 1.31-fold (95% CI 1.18 to 1.46) increased stroke risk in women with AF, especially those aged ≥75 years, regardless of oral anticoagulation (OAC) therapy.[46] Another meta-analysis reported that women with AF have a significantly greater residual risk of cerebrovascular accident/systemic embolism compared with men with AF (odds ratio 1.279, 95% CI 1.111 to 1.473, $p = 0.001$) while on warfarin, but there was no significant gender difference in residual risk of cerebrovascular accident/systemic embolism in patients with AF on novel OACs (odds ratio 1.146, 95% CI 0.97 to 1.354, $p = 0.109$).[47] A meta-analysis analyzing the warfarin arm of 6 studies found that women with AF treated with OAC therapy still had higher stroke rates than men (RR 1.30, 95% CI 1.15 to 1.49, $p < 0.001$).[48] Likewise, there have been several systematic reviews of contemporary data on stroke in women with AF that have found female gender to be an independent predictor of stroke in AF with reported average RRs of 1.5 to 1.9.[49–51]

Comparison of Stroke Risk Stratification Models Regarding Gender: Female gender is increasingly recognized as a stroke risk factor in AF (Table 4). A previously commonly used stroke risk stratification model, $CHADS_2$ (1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points for previous stroke/transient ischemic attack) does not include gender.[52] A large Swedish cohort study found that at each $CHADS_2$ score, the stroke rate was higher in women than in men.[22] In light of the mounting evidence suggesting increased thromboembolic risk in women compared with men, the CHA_2DS_2-VASc (CHA_2DS_2 and 1 point each for vascular disease, age 65 to 74 years, and gender category) model was developed to complement $CHADS_2$ by considering additional stroke risk factors, including female gender, age 65 to 74, and vascular disease.

Several studies support the use of CHA_2DS_2-VASc score, particularly for its additional predictive value for patients with low $CHADS_2$ scores.[31,53] A Danish cohort study reported that CHA_2DS_2-VASc performed better than $CHADS_2$ in identifying patients at high risk and at truly low risk.[19] Likewise, a Chinese AF cohort study found that the 3 new components of CHA_2DS_2-VASc, including age 65 to 74 years, female gender, and a history of other vascular disease, were predictive of stroke in their cohort.[34] A study on postmenopausal women with AF found that for $CHADS_2$ <2, stroke risk almost doubles with each additional CHA_2DS_2-VASc point.[54] A Taiwanese study reported that women with AF with a CHA_2DS_2-VASc score of 1 (no risk factors other than gender) had a 2.5-fold stroke risk compared with men with AF with a score of 0, further validating the additional point for female gender.[21]

That women with AF are at higher risk for thromboembolic events has been highlighted by the recognition and inclusion of female gender as an independent risk factor in newer stroke risk prediction models. However, although there are data to suggest that women with AF are more likely to suffer a thromboembolic event and tend to suffer worse clinical outcomes poststroke than their male counterparts, it has been noted that the more recent the study of excess female risk for thromboembolic events in AF, the lower this risk appears to be. In the 2003 Framingham study,[13] the risk for women was increased by 90%; by 80% in the 2007 Euro Heart Survey[15]; by 50% in the 2005 ATRIA study[36]; and by 47% in the large Swedish cohort study[22] in 2012. This is reflected in the 2012 ESC guidelines stating that women aged <65 years with lone AF are considered low risk and thus, no antithrombotic therapy should be considered. A female patient with AF can have 0 or 2 to 9 points with the CHA_2DS_2-VASc scoring system, as female gender is currently only recognized as a risk factor in the presence of at least one other risk factor.

Reasons Why Stroke Risk in Women May Be Increased: Many reasons have been hypothesized to account for the apparent increased thrombogenicity in women