

Editorial Focus

Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients

Deirdre A. Lane; Gregory Y. H. Lip

University Department of Medicine, City Hospital, Birmingham, UK

Whilst the association between atrial fibrillation (AF) and thromboembolism is well recognised, this risk is not homogeneous. Numerous clinical and echocardiographic factors can be identified that contribute to this risk, and whether or not AF is paroxysmal or sustained (1–2). Female gender poses an intriguing paradigm in relation to the epidemiology of AF and the associated risk of stroke and thromboembolism.

Data from the Framingham Heart Study suggests that the lifetime risk for development of AF is very similar for men and women aged 40 years of age and older, at approximately one in four (3). This risk is analogous to that reported by the Rotterdam Study investigators (4), which found that the lifetime risk associated with developing AF in men and women aged 55 years and above was 23.8% and 22.2%, respectively. The incidence of AF is greater among men at all ages but given that there are almost twice as many women aged ≥ 75 years with AF compared to men, the absolute number of women and men with AF is equivalent (5).

What about gender differences in risk factor profile?

Analyses of the baseline characteristics of the women and men enrolled in the randomised controlled trials (RCT) of thromboprophylaxis for AF (6–9) and epidemiological studies examining AF (10–13) reveal that women and men differ significantly in their AF-presentation, medical co-morbidity, and stroke risk factor profile. Female patients with AF are significantly older (10, 12–14), report more AF-related symptoms (10, 12), are more likely to have pre-existing hypertension (10–12, 14), valvular heart disease (12), heart failure with preserved left ventricular function (12, 14), to have suffered a previous stroke (6), and less likely to have coronary artery disease (6, 10, 14) or diabetes mellitus (6–14) than men. Women also appear to have more risk factors for stroke compared to men (12, 14).

Do women carry an intrinsically higher risk of stroke?

Women are more likely to experience a stroke than men, even at younger ages: women aged 45–54 years have a two-fold increased risk of stroke (odds ratio [OR] 2.39, 95% confidence interval [CI] 1.32–4.32) compared to men of the same age (15). Given that AF is associated with a five-fold increased risk of stroke, do women with AF have a greater propensity for stroke than male AF patients? A recent systematic review (2) of stroke risk factors in AF revealed that 10 studies have examined whether female gender is a risk factor for stroke among AF patients, with half reporting that being female increased the stroke risk. The Atrial Fibrillation Investigators (7) pooled the data from five RCT of patients not on warfarin, revealing that women had a greater tendency for thromboembolism than men (hazard ratio [HR] 1.2; 95% CI 0.8–1.8).

In addition, evidence from patients in the control arms (non-warfarin) of two other RCT of thromboprophylactic therapy in AF patients (6, 9) and epidemiological cohorts (10–13) have demonstrated an increased risk of thromboembolism (6) and/or ischaemic stroke (6, 9, 11–13). The order of magnitude of this risk is approximately 1.6-fold based on RCT evidence (6, 9) and two- to 2.5-fold derived from observational cohorts (11–13), and is independent of age and stroke risk factors (Table 1). The increased risk of stroke among women is not limited to older women, as has been previously suggested (8–9). In the ATRIA study, which was the first RCT with enough endpoints to examine the influence of gender on stroke risk, the risk of thromboembolism was similar among women ≤ 75 and > 75 years (adjusted relative ratio [RR] 1.6, 95% CI 1.0–2.3, and RR 1.8, 95% CI 1.4–2.3, respectively) (6).

Correspondence to:
Dr. Deirdre Lane
University Department of Medicine, City Hospital
Birmingham, UK
Tel.: +44 121 507 5080, Fax: +44 121 507 5907
E-mail: deirdre.lane@swbh.nhs.uk

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Table 1: Risk of thromboembolism and/or ischaemic stroke in women with atrial fibrillation (AF).

Study (reference)	N (% women)	No. of thromboembolic events	Unadjusted risk	Adjusted risk
<i>Randomised controlled trials</i>				
AFI (7)	3,432 (34)	91 events (81 ischaemic strokes)	1.2 (0.8–1.8)*	
ATRIA (6)	13,559 (43)	394 events (369 ischaemic strokes)	1.9 (1.6–2.4)†	1.6 (1.3–1.9)† for thromboembolism 1.5 (1.2–1.8)† for ischaemic stroke
SPAF (9)	2,012 (28)	130 ischaemic strokes	‡	1.6 (‡); p=0.01
<i>Observational studies</i>				
Framingham (13)	2,844 (48)	83 ^a ischaemic and haemorrhagic strokes	‡	1.92 (1.20–3.07)*
Euro Heart Survey (12)	5,333 (42)	87 ischaemic strokes	‡	1.83 (1.10–3.03)**
Copenhagen City Heart Study (11)	29,310 276 (40) AF	35 strokes		2.6 (1.3–5.4)*

* hazard ratio; ** odds ratio; † relative risk; ‡ not reported. ^a warfarin-censored patients. ^b calculated based on 2.2% stroke rate vs. 1.2% in women & men, respectively. AFI – Atrial Fibrillation Investigators; ATRIA – AnTicoagulation and Risk factors in Atrial fibrillation; SPAF – Stroke Prevention in Atrial Fibrillation.

Why are women at increased risk of thromboembolism and stroke?

This increased risk may be due, in part, to the greater prevalence of hypertension among women with AF, given that lowering blood pressure is associated with a significant reduction in vascular events (16). Numerous other possible mechanisms to explain gender differences in AF-related thromboembolic risk have been proposed, including differences in the structure and function of the left atrium (17), and endothelial damage/dysfunction and markers of platelet activation (18). In the Rotterdam study, there was a positive linear relationship between von-Willebrand-factor level and presence of AF which remained significant after adjustment for potential confounders among women (OR 1.17; 95% CI 1.02–1.34) per 10-IU/dl increase in von-Willebrand-factor but not among men (OR 1.06; 95% CI 0.96–1.17) (18).

It has also been suggested that estrogen replacement therapy increases the risk of ischaemic stroke among post-menopausal women (19); however, such therapy was not associated with greater risk of thromboembolism (RR 1.0; 95% CI 0.7–1.4) in multivariate analyses in the ATRIA study (6). Further, physicians often have a fear of an increased risk of bleeding in older people, particularly older women (20–21) and consequently oral anticoagulants may be prescribed less frequently to the very people who stand to benefit the most from them. The evidence regarding gender differences in the prescription of warfarin is inconsistent, with some studies reporting that women, especially older women, are less likely to receive warfarin than men following a stroke (10, 22–24). Although the recent Euro Heart Survey of AF (12) and other studies (14) did not demonstrate any difference in the prescription of oral anticoagulants between women and men at baseline.

Does oral anticoagulant therapy reduce the risk of thromboembolism amongst women?

There is overwhelming evidence of the benefit of dose-adjusted warfarin in the reduction in thromboembolic events for AF patients compared to placebo or anti-platelet agents (25). However, the meta-analysis of these trials did not examine gender differences in thromboprophylaxis.

In the February 2009 issue of *Thrombosis and Haemostasis*, Poli et al. (26) examined whether female gender was a risk factor for stroke among 780 (35.3% women) AF patients receiving oral anticoagulant therapy, and whether there were differences in the quality of this treatment and major bleeding between the sexes. This prospective study demonstrated that there were no significant gender differences in international normalised ratio (INR) control: the proportion of time the INR was therapeutic (71% in females vs. 70% for males), below 2.0 (14% in females vs. 15% in males) and over 3.0 (15% in females vs. 14% in males) was similar in women and men (26), a finding consistent with previous research (14).

The excellent therapeutic INR control, outside of a clinical trial setting, seen in that study (26) is very encouraging given that a recent systematic review revealed that patients who receive long-term oral anticoagulants achieve a therapeutic INR only 55% of the time (27). Maintenance of this narrow therapeutic INR range is important given that there is an increased risk of haemorrhagic stroke with INR >3.0 and thromboembolic complications at INR <2.0 (28–29).

In addition, Poli et al. (26) found no significant difference in major bleeds between women and men (1.3% vs. 1.4%, respectively; p=1.00), a finding consistent with previous research (6, 12). In the ATRIA study (6), the first RCT powered to examine

the interaction of female gender and warfarin on major haemorrhage, women were less likely to develop intracranial haemorrhage while on warfarin in multivariate analyses (0.36% vs. 0.55%; adjusted RR 0.5, 95% CI 0.3–0.9). This finding was further confirmed by the Euro Heart Survey on AF (12), which found that although women had a significantly higher rate of major bleeding (2.2% vs. 1.3%; $p=0.028$) in univariate analyses, this risk was abolished after adjustments were made for age, comorbidities, and treatment (OR 1.28, 95%CI 0.76–2.13; $p=0.35$). Two of the four published bleeding risk stratification models consider female gender as an important risk factor for inclusion in their risk schema (30). Bleeding risk is an extremely important consideration, as we do not want to cause more major bleeds which may be catastrophic for the patient, in order to reduce the risk of ischaemic stroke.

However, despite the similarity in the quality and control of oral anticoagulant therapy, and parallels in CHADS₂ stroke risk profiles, women were almost three times as likely to experience an ischaemic event (2.4% vs. 1.2%, $p=0.04$) on oral anticoagulants compared to men (OR 2.9; 95% CI 1.5–5.6; $p=0.002$) (26) after adjustment for age, sex, previous ischaemic event, and hypertension. The INR value was not related to the thromboembolic events. In addition, when a stroke occurred it was three times more likely to be fatal or severely disabling in women (HR 3.1, 95% CI 1.3–6.5; $p<0.01$). This finding is similar to increased risk of stroke among women in the Euro Heart Survey (2.2% vs. 1.2%; $p=0.011$) adjusted for age and stroke risk (OR 1.83; 95% CI 1.10–3.03; $p=0.019$) (12), but at odds with other research (6–7, 14, 31). In the ATRIA study (6), the unadjusted RR of thromboembolism on warfarin was similar among men and women (1.2% and 1.5%, respectively); however, in multivariate analyses, warfarin was associated with a significant reduction in thromboembolic risk for both men and women (men: RR 0.6, 95% CI 0.5–0.8, and women: RR 0.4, 95% CI 0.3–0.5, respectively) (6).

Although encouraging with regard to quality of INR control and similar risk of major bleeding in men and women, the results from the prospective observational study by Poli et al. (26), in respect to greater thromboembolic risk among women, should be interpreted with some caution, given that the study was probably underpowered to examine the contribution of female gender to risk of thromboembolism (given the low event rate) among those patients on warfarin. This study should not discourage physicians from prescribing oral anticoagulant therapy to women.

The cynic would argue that the data concerning a greater risk of thromboembolism and bleeding risk among female AF patients is somewhat conflicting. This is reflected in the exclusion of female gender from the list of main stroke risk factors in the majority of risk stratification schemes (2). Only the SPAF (32), Framingham risk score (13), and AFI (7) include female gender in their risk stratification schemes, and female gender is only included as a “less validated or weaker risk factor” in the revised ACC/AHA/ESC guidelines (33). Obviously, the variations between the stroke risk stratification schemes can cause confusion and influence a physicians’ decision to initiate/continue oral anticoagulation therapy, resulting in many patients who would potentially benefit from oral anticoagulants not being prescribed them.

Conclusion

The balance of evidence suggests that female gender is an independent risk factor for stroke and thromboembolism. Compared to men, women are more likely to suffer a thromboembolic event or ischaemic stroke when not taking warfarin, but when they are prescribed warfarin they have comparable INR control, are not more likely to suffer a major bleed, and demonstrate a greater thromboembolic risk reduction. Therefore, women should be prescribed oral anticoagulation therapy when appropriate, after stroke risk stratification and bleeding risk assessment.

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