Female sex as an independent risk factor for stroke in atrial fibrillation: Possible mechanisms

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Summary
Atrial fibrillation (AF) is an independent risk factor for thromboembolism and stroke. Women with AF are at a higher overall risk for thromboembolic stroke when compared to men with AF. Recent evidence suggests that female sex, after adjusting for stroke risk profile and sex differences in utilisation of anticoagulation, is an independent stroke risk factor in AF. The inclusion of female sex has improved the accuracy of the CHADS2 stroke risk stratification schema (Congestive heart failure, Hypertension, Age 75 years or greater, Diabetes mellitus, and prior Stroke or TIA). The newly revised and validated schema, CHA2DS2-VASc, dichotomises age and incorporates female sex and vascular disease history. The pathophysiological mechanisms to explain this increased risk in women are not well understood. According to Virchow’s triad, thrombosis that leads to stroke in AF should arise from three co-existing phenomena: structural abnormalities, blood stasis, and a hypercoagulable state. Herein, we explore the sex differences in the biological processes that lead to thrombus formation as applied to Virchow’s Triad. The objective of this review is to describe the potential mechanisms behind the increased risk of stroke in AF associated with female sex.

Keywords
Atrial fibrillation, stroke, sex differences, anticoagulation

Introduction
Women are at a higher overall risk of thromboembolic stroke than men (1) and suffer more disability in association with stroke (2). Atrial fibrillation (AF) is an independent risk factor for thromboembolism and stroke (3) and although conflicting data exist, the balance of evidence suggests that female sex, after adjusting for stroke risk profile, is associated with a higher risk of stroke in the setting of AF (4–6). Underutilisation or inadequate oral anticoagulation in women could potentially explain part of these sex-differences in stroke risk (7–10). However, a more recent study found a persistently higher risk of stroke among women as compared to men despite similar warfarin adherence rates (11). Here we review the evidence and investigate the potential factors contributing to what appears to be an intrinsically higher risk of stroke in AF associated with female sex.

General mechanisms of thromboembolism in AF
In 1856, Rudolf Virchow postulated that thrombosis arises from three co-existing phenomena: abnormalities in the vessel wall, blood stasis, and a hypercoagulable state (12). Virchow’s triad can be applied to thrombogenicity in AF (Figure 1). As illustrated by Watson, Shantsila and Lip, structural changes in the left atrium (LA) and left atrial appendage (LAA), blood stasis induced by left atrial dilatation and inhibited forward flow, and the prothrombotic milieu constitute Virchow’s triad in AF (13). The LA, specifically the LAA, is the most common site of intracavitary thrombus formation in patients with and without AF (14). The LAA is a long, thin chamber with a narrow apex and an inner surface of muscular ridges that takes on multiple anatomic characteristics (15). In patients with AF, advanced endothelial changes can be appreciated by scanning electron microscopy, which include cellular perforations and large crater-like areas that attach fibrin plaques and platelet clumps (16). Boldt et al. noted increased deposition of col-

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lager I, collagen III, and fibronectin (all part of the extracellular matrix [ECM] and increased fibrosis) in LA tissue of patients with AF compared to those in normal sinus rhythm (17). Further, patients with AF have impaired ECM degradation, illustrated by abnormal plasma concentrations of both metalloproteinases and their inhibitors (18). Other changes in atrial tissue in patients with AF include myocyte necrosis or hypertrophy as well mononuclear cell infiltrates (19). These structural changes are significant contributors to the thrombogenicity of AF (20).

LA enlargement in AF leads to changes in blood flow, which can be visualised on transesophageal echocardiogram as spontaneous echo contrast (SEC). SEC, also known as echogenic “smoke,” appears to be due primarily to the interaction of red blood cells and plasma proteins at low flow and low shear rate conditions, and can be a manifestation of a prothrombotic condition in AF (21, 22). The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators found that the presence of SEC in the LA or LAA and LA dilatation (after adjusting for body surface area) were both independent risk factors for stroke in patients with AF at high stroke risk (23, 24).

As a consequence of structural and blood flow changes, prothrombotic conditions develop with activation of coagulation proteins. Indeed, concentrations of prothrombotic factors, such as prothrombin fragment 1+2 and thrombin-antithrombin complexes, have been found elevated in stroke patients with AF as compared to stroke patients without AF (25). D-dimer is also associated with a heightened risk of thromboembolic events in patients (including those on warfarin) with non-valvular AF (26–29). Von Willebrand factor has also been associated with AF in the Rotterdam study (30), and more specifically, LAA thrombus (31). Because the blood shear conditions developing in the LA favour the stimulation of the coagulation factors and fibrin formation, establishing a link between altered platelet function and AF has been more elusive. Yet there is consensus that β-thromboglobulin, a marker of platelet activation and subsequent thrombogenesis, is increased in patients with AF (32–34).

**Evidence for female sex as an independent risk factor for stroke in AF**

Diverse stroke risk stratification schemes have been proposed to quantify stroke risk in patients with AF (35, 36) based on different consensus groups’ analyses of relevant data, including the Atrial Fibrillation Investigators (37), SPAF Investigators (38), the Birmingham/National Institute for Health and Clinical Excellence (NICE) (39), the American College of Chest Physicians (40), and the Framingham Heart Study (41). Of the various schemes, the CHADS2 score is widely used and based on the risk factors: Congestive heart failure, Hypertension, Age 75 years or greater, Diabetes mellitus, and prior stroke or transient ischaemic attack (TIA) (42). Female sex has not consistently been included in risk stratification models, but was noted to independently confer elevated risk by the SPAF Investigators (relative risk [RR] 1.6, p=0.01) (43). When the Atrial Fibrillation Investigators combined data from five randomised trials (AFASAK, SPAF, BAATAF, CAFA, and SPI-NAF), they found that within the control group (not on warfarin), women demonstrated a trend towards a higher risk of stroke than men (RR 1.2; 95% confidence interval [CI] 0.8–1.8) (37). Several observational studies have found female sex to be an independent stroke risk factor among individuals with known AF. After adjusting for the higher burden of hypertension and prior stroke in women, the Framingham Heart Study, the Euro Heart Survey, the Copenhagen City Heart study, and the Anticoagulation and Risk

![Figure 1: Rudolf Virchow postulated that the pathophysiology of thrombus formation forms a triad which includes abnormalities of the vessel wall, blood stasis, and a hypercoaguable state. This triad can be applied to thrombus formation in atrial fibrillation, where the structural change occurs at the left atrial appendage, undergoing a resultant hypercoaguable transformation due to increased blood stasis and an inflammatory milieu. ECM, extracellular matrix; vWF, von Willebrand factor; RBC, red blood cell.](image-url)
Factors in Atrial Fibrillation cohort reported that female sex conferred relative risks of stroke of 1.92 (95% CI 1.20–3.07), 1.83 (95% CI 1.10–3.03), 2.6 (95% CI 1.3–5.4), and 1.6 (95% CI 1.3–1.9), respectively, among patients with AF (4, 5, 41, 44) (Table 1). Inclusion of female sex has been shown to improve the accuracy of the CHADS2 schema (45). Lip et al. revised the Birmingham 2006 stroke risk stratification schema by dichotomising age and incorporating vascular disease and female sex, creating the CHA2DS2-VASc (Congestive Heart Failure, Hypertension, Age ≥ 75 [doubled], Diabetes, Stroke [doubled] – Vascular disease, Age 65–74, and Sex category [female]). This schema had a better predictive value when compared to CHADS2, among patients enrolled in the Euro Heart Survey for AF (C statistic=0.61 vs 0.56, respectively), and may be especially useful in determining risk in lower-risk patients. The CHA2DS2-VASc has been incorporated into the European guidelines for use in stroke risk stratification (46, 47).

### Table 1: Adjusted risk of female sex in major stroke in atrial fibrillation studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Women (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI [37]</td>
<td>1994</td>
<td>34</td>
<td>1.2</td>
<td>0.8–1.8</td>
<td>----</td>
</tr>
<tr>
<td>SPAF [43]</td>
<td>1999</td>
<td>28</td>
<td>1.6</td>
<td>1.2–2.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Framingham [41]</td>
<td>2003</td>
<td>47</td>
<td>1.7</td>
<td>1.3–5.4</td>
<td>----</td>
</tr>
<tr>
<td>Copenhagen Heart Study [5]</td>
<td>2004</td>
<td>56</td>
<td>2.6</td>
<td>1.3–1.9</td>
<td>----</td>
</tr>
<tr>
<td>ATRIA [4]</td>
<td>2005</td>
<td>43</td>
<td>1.6</td>
<td>1.1–3.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Euro Heart Study [44]</td>
<td>2007</td>
<td>42</td>
<td>1.8</td>
<td>1.1–3.0</td>
<td>----</td>
</tr>
<tr>
<td>SPAF, Stroke Prevention in Atrial Fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; AFI, Atrial Fibrillation Investigators. RR, relative risk; CI, confidence interval.</td>
<td></td>
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</tbody>
</table>

Potential mechanisms for higher stroke risk in women with AF

**Hormone therapy and menopause**

The risk for ischaemic stroke in women doubles between the ages of 55 and 65, the menopausal transition period during which oestradiol levels decrease by about 60% (48–50). Endogenous oestrogen has favourable outcomes on lipid metabolism, coagulation and vascular tone, and even incident AF, but evidence is mixed on the association of endogenous oestrogens with the risk of cardiovascular disease (CVD), and stroke in particular (51, 52). In a meta-analysis of seven major randomised trials analysing hormone therapy (HT) [including the Women's Health Initiative (WHI) and Women's Estrogen for Stroke Trial (WEST)], Magliano et al. reported an increased risk of stroke in both combination HT trials and estrogen-only trials (RR 1.29, 95% CI 1.06–1.56 and RR 1.30, 95% CI 1.07–1.57, respectively) (53). Further, Viscoli from the WEST investigators found that the administration of estrogen replacement therapy after an incident ischaemic stroke was associated with a two-fold increased risk of stroke during the first six months after randomisation (RR 2.3, 95% CI 1.1–5.0, p=0.03) (54).

Among patients with AF, observational assessments of HT use have been inconsistently associated with elevations in stroke risk. Similar to the results in the WEST and WHI trial populations, HT among women with AF in the SPAF trial populations was associated with higher rates of ischaemic stroke after adjustment for the independent stroke risk factors (RR 3.2, p=0.007), including female sex (55). On the contrary, no association with HT and stroke was found amongst the ATRIA study population with AF (4). In observational studies, time-dependent risks of new HT use may be obscured by cross-sectional ascertainment of prevalent estrogen use at baseline. This is particularly relevant given that risk may be conferred by fluctuating levels and not baseline hormone levels (51).

Although HT has some known protective effects on the cardiovascular system, it is synthetic and not biologically identical to premenopausal endogenous hormones. HT has significant pro-thrombotic effects including an upregulation of coagulation factors and downregulation of anti-coagulant proteins (56). The overall effect of HT on risk of stroke in women with AF is likely a balance between its protective and prothrombotic factors that also needs to account for individual fluctuations in baseline endogenous estrogen levels. The decline in endogenous estrogen receptors, as occurs in menopause, contributes to an upregulated production of inflammatory cytokines, especially in the cerebral vasculature, which further contributes to this “hypercoagulable state” (57, 58). The role of inflammation is discussed in more depth in a subsequent section.

**Sex differences in haemodynamics and cardiovascular remodelling**

Changes in haemodynamics and structural changes in the left ventricle have been well-defined in post-menopausal women. Women who enter their seventh to eighth decade of life typically have higher blood pressures (BP) than men (59). Isolated systolic hypertension and elevated pulse pressure (systolic BP – diastolic BP) are clinical manifestations of vascular stiffness (60). Prior to their seventh decade of life, women have a lower pulse pressure than men, but this difference reverses and pulse pressure continues to increase in women through the ninth decade. This pulse pressure pattern was reported in both the hypertensive and non-hypertensive cohorts of the Framingham Heart Study (59). Elevated pulse pressure is associated with underlying arterial stiffness, which is marked by collagen deposition, elastin degradation, and wall thickening with eventual dilatation (61). Altered pulse wave velocity, a marker of arterial stiffness, has been associated with increased risks of stroke and CVD mortality (62). Redfield et al. found that the effective arterial elastance index (EaI)—a measure influenced by systemic vascular resistance, heart rate, and central aortic stiffness—was much higher in women than in men (63). As women age, one would anticipate increased BP variability as a result of these changes. One recent study showed that visit-to-visit variability (VVV) in BP, after adjusting for cardiovascular risk fac-
tors, was associated with increased risk of stroke in post-menopausal women (64).

Post-menopausal women compared to pre-menopausal women not only have blunted nocturnal decreases in systolic and diastolic BP and higher peripheral vascular resistance, but also have greater left ventricular wall thickness (65). Compared to men, women from the Framingham Heart Study more often present with diastolic heart failure with preserved ejection fraction (HFrEF) with an age-adjusted odds ratio (OR) of 2.55 (95% CI 1.77–3.68, p<0.001) (66). The impaired relaxation of the left ventricle renders it less compliant in the face of increases in blood volume or vascular tone (67). The resultant increase in pressure is transmitted to the atrium thereby inducing atrial strain and dysfunction. This finding is relevant in AF, since heart failure has been associated with higher stroke rates (35, 36, 41), and one study found similar rates of stroke in heart failure patients with EF <35% vs EF>50% (68). HFrEF has also recently been found to be an independent risk factor for stroke in AF (69). These haemodynamic and structural differences are supported further by the higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in women compared to men across age and degree of heart failure (70–72). Recently NT-proBNP and troponin I were shown to be associated with an increased risk of stroke in AF, independent of CHA2DS2-VASc score (73).

Prothrombotic and inflammatory biomarkers, platelet aggregation and the hypercoagulable state

Evidence in mice suggests that with age-related reproductive senescence, phenotypic changes in platelet function occur resulting in greater propensity for blood thrombogenicity. Studies in mice with deletion of the beta estrogen receptor in platelets, a phenomenon that occurs in females with age, reveal an increase in fibrinogen receptors and procoagulant surface expression of P-selectin (74), and likely enhanced platelet-monocyte aggregation via increased tissue factor expression. Enhanced platelet-monocytic aggregate formation has recently been linked to greater ischaemic stroke severity and recurrent vascular events (75). In addition, platelet beta oestrogen receptors are protective in oxidative stress yet they become deficient in post-menopausal mice. This results in a loss of platelet viability and increased potential for shedding of thrombogenic microparticles (76).

Von Willebrand factor is known to be a contributing factor to thrombogenesis in the LAA in patients with AF (77, 78). Data from the Rotterdam Study suggests that the presence of AF is associated with higher levels of von Willebrand factor in women but not in men (OR 1.17, 95% CI 1.02–1.34) (30). As previously mentioned, D-dimer and β-thromboglobulin levels are also associated with increased thrombogenicity in AF; however, it is unclear from current evidence if this relationship is greater in women.

Risk factor reduction and control

In addition to potential sex-differences in biological mechanisms, there is a higher burden of stroke risk factors among women with AF compared to men and less optimal treatment and control of these risk factors. For instance, in several analyses of sex differences in stroke risk, women with AF were older and more likely to be hypertensive (4, 11, 79, 80). Of participants in the SPORTIF III and V trials, women had a larger number of associated thromboembolic risk factors (43% vs 38% with three or more risk factors in addition to AF; p<0.0001) when compared to men (79). Sex differences in age-related cardiovascular mortality may also be contributing to these observations (81). A recent analysis of more than one million deaths reported to the Finnish Causes of Death Register found the age-standardised risk of cardiovascular death to be 80% higher for men, highest amongst those 45 to 59 years of age. Because men die younger of cardiovascular disease, the greater burden of AF and AF-related risk factors among older women may to some degree reflect this natural selection (82).

Sex differences in medication effects on thrombogenesis in patients with AF are evident and create an area for future study. For instance, in a subanalysis of the Rate Control Versus Electrical Cardioversion (RACE) trial, women randomised to rhythm control more frequently encountered heart failure and thromboembolic complications as compared to females randomised to rate control despite comparable baseline characteristics. This difference was not observed in men (80). Sex differences also exist in overall stroke risk factor reduction, management, and outcomes as illustrated by the data from the North East Melbourne Stroke Incidence Study (NEMESIS) and the Swedish Stroke Register (83, 84). It is evident that females experience suboptimal risk factor reduction and control, which suggests that in addition to biological differences there also exist differences in diagnosis and treatment between sexes; for example, females are less likely to receive beta-blockers and lipid-lowering therapy prior to stroke onset (83). Further, the Women's Health Initiative found that only 64.3% of hypertensive women in their study were on BP lowering medications and overall adequate BP control was achieved in only 36.1% (85).

Women with AF are less likely than men to be prescribed an oral anticoagulant (83). Women are also less likely than men to receive thrombolytic therapy within the three-hour window of an acute stroke, even after adjusting for confounders (86). For those women who are treated with oral vitamin K antagonists, several studies have demonstrated suboptimal time in the therapeutic range compared to men with AF (87, 88). The NEMESIS study reported sex differences in post-stroke management, future risk reduction, and post-stroke morbidity independent of baseline anticoagulant and antiplatelet use. Women presented with stroke, on average, four years later than men. In addition, they had more severe stroke symptoms, such as dysphasia, visual deficits, and loss of consciousness, and at three months, had greater physical and mental impairment. Lastly, post-stroke, fewer echocardiographic evaluations and carotid artery Doppler studies were performed in women compared to men, but this difference decreased in magnitude when adjusted for age, stroke severity, and baseline functional status (83).
Conclusion

Existing scientific evidence documents several potential mechanisms to explain the observed higher risk of ischaemic stroke among women with AF compared to men. Sex-related differences in the vasculature and myocardial structure may predispose to alterations in blood flow, shear stress, and altered endothelial function. Further, there is evidence suggesting a potential sex-based increase (especially in the post-menopausal state) in inflammatory and procoagulant markers, thrombogenic particles and platelet aggregation, all of which contribute to a prothrombotic milieu. Observational data suggest sex-based differences in stroke outcomes are related to differences in stroke risk factor profile and management, in addition to underutilisation of anticoagulant therapy in women. However, recent study results demonstrate an increased stroke risk in women despite baseline anticoagulant use. Future challenges in research will be to better understand the interplay of the hypothesised biological mechanisms with sex, to identify strategic points in targeted pathways amenable to intervention, and to better elucidate the complex role of endogenous estrogen on the vasculature, platelets, and haemostatic proteins. Importantly, evidence suggests that deleterious fundamental changes ensue following menopause, which highlights the need to specifically address the aging female population 65 years and older (89). In the interim, given this heightened risk of stroke among women with AF, stroke preventive therapy and risk factor reduction remain paramount.

Conflicts of interest

Dr. Cove and Badimon report no conflicts of interest. Dr. Albert is a consultant for GlaxoSmithKline. Dr. Andreotti is speaker or consultant for Amgen, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Pfizer. Dr. Van Gelder is a consultant for Sanofi-Aventis, Boehringer Ingelheim, and Cardiome. Dr. Hylek is a consultant for Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, and Pfizer.

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Cove et al. Female sex as an independent risk factor for stroke in AF


