JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 72, NO. 3, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Sex Implications in the Response to Anticoagulant Therapy in Atrial Fibrillation*

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Men are from Mars
Women are from Venus (1)

Thromboembolic risk related to atrial fibrillation (AF) may differ between men and women, and this may affect the response to anticoagulant therapy and warrant a sex-specific management of patients with AF. Sex-related differences have been reported in thrombotic and hemorrhagic burdens: these include multiple factors involved in endothelial function, platelet aggregation, and coagulation mechanisms in various vascular beds, partly related to the hormonal status at various ages in women. Particularly, hormonal changes modify the levels of coagulation factors during the normal menstrual cycle, and changes in coagulation have been reported with pregnancy, postmenopause, oral contraceptive use, and oral administration of synthetic estrogens as hormone replacement therapy (2) (**Table 1**). In general, the higher female hormone levels are, the higher the activation of coagulation is. On the other hand, bleeding risk also seems to be higher in women, and impacts on the risk of future cardiovascular events and on mortality (3). The higher risk of bleeding has been partly explained by inappropriate dosing of antithrombotic agents (4), mainly related with the women's lower body weight, against no difference in dose recommendations according to sex. Benefits of antithrombotic therapy may differ in women compared with men in various clinical settings, in both primary and secondary prevention of cardiovascular disease, and according to the type of antithrombotic agent used (5). Against this background, it is conceivable that sex differences in thromboembolism and bleeding exist in AF, leading to a prothrombotic state. The response to antithrombotic therapies in this condition may also differ in women compared with men.

AF is an independent risk factor for stroke: this risk is particularly high in patients with mitral stenosis or mechanical prosthetic valves, currently demanding therapy with vitamin K antagonists (VKAs), such as warfarin, while for all the other patients thromboembolic risk varies from very high to very low, in this latter case at levels similar to the population without AF. In such patients, assessing thromboembolic risk over time is crucial to optimize antithrombotic therapy. Current guidelines recommend estimating thromboembolic risk in patients with AF based on a clinical risk-stratification scheme, mostly the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled]-vascular disease, age [65 to 74 years], and sex [female]) score (6). As female sex independently increases the risk of stroke in AF, particularly in older women, when other risk factors are present, female sex is currently recognized as a "risk factor modifier" (7), in that it does not appear to increase stroke risk in the absence of other risk factors (8). For these reasons, female patients without other risk factors do not need antithrombotic therapy, and oral anticoagulation is recommended for patients with CHA_2DS_2-VASc score ≥1 if men, and ≥2 if women (6).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.05.015

TABLE 1 Coagulation in Women: Main Changes of Coagulation Factors and Anticoagulant Factors According to Hormonal Status Associated With Menstrual Cycle, Pregnancy, Hormone-Based Contraceptives, and HRT

Coagulation Parameters	Menstrual Cycle	COC*	Pregnancy	HRT†
VWF	Fluctuations in VWF:Ag and VWF:Ac: trough levels at days 9–10 of the cycle; peak levels at days 23–24 of the cycle	No variations in VWF	↑ VWF	↑ VWF
Fibrinogen	Fluctuations in fibrinogen: increase in luteal phase and return to baseline at the beginning of the cycle	↑ fibrinogen	↑ fibrinogen	
Coagulation factors	Fluctuation in factor VII: lower during midcycle and luteal phases vs. follicular phase	↑ factor VII ↑ factor X	↑ factor VII ↑ factor VIII ↑ factor X ↑ factor XII	↑ factor VII ↑ factor IX ↑ factor X ↑ factor XII ↑ factor XIII ↑ Prothrombin fragments 1+2
PT	Changes in PT (INR): higher during the midcycle and luteal phases vs. follicular phase		↓ PT (INR)	
Anticoagulant factors and activity	Changes in AT: lower during the midcycle vs. luteal phase and follicular phase Changes in t-PA: lower during the luteal phase vs. follicular phase	↓ AT ↓ protein S ↑ protein C ↑ plasminogen ↑ APC resistance	↓ protein C ↓ protein S ↑ PAI ↑ alpha-2-antiplasmin ↑ D-dimers ↑ APC resistance	↓ AT ↓ protein C ↓ protein S ↓ tissue factor pathway inhibitor ↑ APC resistance

*Differences between combined oral contraceptives (COC) generations. †Differences between estrogen doses and administration route.

↑ = increase; ↓ = decrease; APC = activated protein C; AT = antithrombin; HRT = hormone replacement therapy; INR = international normalized ratio; PAI = plasminogen activator inhibitor; PT = prothrombin time; t-PA = tissue plasminogen activator; VWF:Ac = von Willebrand factor activity; VWF:Ag = von Willebrand factor antigen.

Outcomes of women with AF also markedly differ from men, and women with AF have a higher mortality, even after adjusting for baseline comorbid conditions and treatment with anticoagulants, although these data are inconsistently reported in the literature (9).

The clinical effectiveness of oral anticoagulants, such as VKAs and the newer direct oral anticoagulants (DOACs) has been established by well-designed clinical trials, but the impact of sex and sex-associated differences in risk factors for thromboembolism, and on outcomes of anticoagulant treatment in patients with AF, is not fully understood. Inconsistent reports have been indeed derived from observational and prospective cohort studies evaluating sex differences in clinical outcomes of anticoagulated patients, mainly referred to the VKA era. Overall, the use of anticoagulant therapy for stroke prevention has resulted not to be different in men and women, although on average women enrolled in such studies were older than men and had a higher prevalence of comorbidities (10). Nevertheless, in the GARFIELD-AF (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) registry, the risk of stroke or systemic embolism was apparently lower with anticoagulant therapy in men than in women compared with no anticoagulant treatment (9). The lower impact of anticoagulant treatment on stroke rates in women has been ascribed to a poorer anticoagulation control when women are treated with VKAs, partly explained by a lower weight—implying wider swings in anticoagulation control at the beginning of therapy, a different hepatic metabolism of warfarin by cytochrome P450 enzymes—higher bioavailability after oral drug dosing, for CYP3A substrates in particular, a lower adherence to therapy, a higher age, or the use of lower doses and target ranges in women compared with men.

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Few data are available on the comparative effectiveness of DOACs in male versus female patients with AF. Data pooled from the 4 phase III clinical trials in the meta-analysis by Ruff et al. (11) showed that the benefit of DOACs versus warfarin in reducing stroke or systemic embolism was consistent in men and women, as was the lower incidence of major bleeding. In this issue of the *Journal*, Law et al. (12) readdress this issue, comparing effectiveness and safety outcomes of DOACs versus warfarin in men and women after stratifying for anticoagulation control. The authors conducted a population-based cohort study collecting data from electronic medical records of the Clinical Data Analysis and Reporting System in Hong Kong, and identified patients with a new diagnosis of AF between 2010 and 2015. They defined a