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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).

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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.

SEE PAGE 271

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

composite of ischemic stroke or systemic embolism (SSE) as a measure of effectiveness as the primary outcome, and intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality as secondary safety outcomes. Here, DOAC use was associated with a lower risk of ICH and all-cause death compared with warfarin in women but not in men, although the relative risk of SSE with DOACs versus warfarin was comparable. Furthermore, and notably, the lower risk of ICH in the women cohort associated with the DOACs remained significant regardless of the quality of the anticoagulation control in warfarin-treated patients taken as a control. On the other hand, a lower risk of GIB, as well as a lower risk in SSE and all-cause mortality, both in men and women treated with DOACs, was observed in the comparison with warfarin users without a routine international normalized ratio control.

Other similar signals towards a potential sex difference in clinical outcomes in patients treated with DOACs come from other 2 meta-analyses of phase III clinical trials, both indicating significantly less major bleeding in women compared with men (13,14), with a similar (13) or higher (14) risk for stroke or systemic embolism in men compared with women. Conversely, two recent observational studies indicated that the reduced risk of ischemic stroke in patients taking rivaroxaban compared with dabigatran and warfarin seems to be limited to men, whereas the higher risk of bleeding seems to be limited to women (15). Men were also observed to have more benefits from dabigatran treatment by having less bleeding compared with warfarin (16).

The inconsistency of published results is probably due to the different nature of trials, meta-analyses or observational studies, different study designs, patient selection, inclusion criteria, outcomes, and durations of follow-up. Particularly, Law et al. (12) collected data from electronic medical records of patients with predominantly Asian ethnicity. As an efficacy outcome, they included ischemic stroke only, at variance from other papers in which stroke included both ischemic and hemorrhagic strokes. In addition, they separately considered ICH and GIB as safety outcomes, which are not directly comparable with major bleeding overall, as it has been more often evaluated in the assessments of interactions of safety with sex elsewhere. Finally, although propensity score matching was used, residual confounders might have affected the results, because of the nonrandomized nature of their study.

In any case, the main finding from the study by Law et al. (12), as well as from other studies, points to the existence of sex difference in thrombotic and hemorrhagic risk and in the response to anticoagulants. This may imply different efficacy and safety profile of the DOACs in patients with AF according to sex, which should be confirmed in further studies. Further studies are also needed to fully elucidate the mechanisms underlying sex differences, eventually to help clinicians to make the best of anticoagulants in general, and of DOACs in particular, also according to sex.

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REFERENCES

1. Gray J. Men Are from Mars, Women Are from Venus. New York, NY: HarperCollins Publishers Inc., 2012.

2. Trigg DE, Wood MG, Kouides PA, Kadir RA. Hormonal influences on hemostasis in women. Semin Thromb Hemost 2011;37:77–86.

3. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003;24:1815–23.

4. Ahmed B, Piper WD, Malenka D, et al. Significantly improved vascular complications among women undergoing percutaneous coronary intervention: a report from the Northern New England Percutaneous Coronary Intervention Registry. Circ Cardiovasc Interv 2009;2:423–9.

5. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006;295:306–13.

6. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

7. Cove CL, Albert CM, Andreotti F, Badimon L, Van Gelder IC, Hylek EM. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. Thromb Haemost 2014;111:385–91.

8. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM 2014;107:955–67.

9. Camm AJ, Accetta G, Al Mahmeed W, et al. Impact of gender on event rates at 1 year in patients with newly diagnosed non-valvular atrial fibrillation: contemporary perspective from the GARFIELD-AF registry. BMJ Open 2017;7:e014579.

10. Lip GY, Rushton-Smith SK, Goldhaber SZ, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. Circ Cardiovasc Qual Outcomes 2015;8:S12–20.

11. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral

anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.

12. Law SWY, Lau WCY, Wong ICK, et al. Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation. J Am Coll Cardiol 2018;72:271–82.

13. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. Am J Cardiol 2014;113:485–90.

14. Proietti M, Cheli P, Basili S, Mazurek M, Lip GY. Balancing thromboembolic and bleeding risk with non-vitamin K antagonist oral anticoagulants (NOACs): A systematic review and meta-analysis on gender differences. Pharmacol Res 2017;117:274–82.

15. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 2012;307:1952–8.

16. Palamaner Subash Shantha G, Bhave PD, Girotra S, et al. Sex-specific comparative effectiveness of oral anticoagulants in elderly patients with newly diagnosed atrial fibrillation. Circ Cardiovasc Qual Outcomes 2017;10:e003418.

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