

Sex Differences of Oral Anticoagulant Therapy in Atrial Fibrillation

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Atrial fibrillation (AF) is a growing epidemic affecting mainly older people. Approximately 70 % of individuals with AF are between 65 and 85 years of age. The prevalence of AF is lower in females compared to males. However, the average life expectancy of females is 5.5 years higher compared to males which makes AF a significant problem of older women. After age 75 years, about 60 % of the people with AF are women [1].

The risk of stroke in women is higher in women with AF compared to men. Namely, the Copenhagen City Heart Study has shown that women with AF had a much higher risk of stroke than women without AF (HR 9.1). Men with AF were also at increased risk of stroke compared with men without AF (HR 2.0), but the effect of AF on the risk of stroke was 4 times greater in women than in men (HR 4.5). In addition, the effect of AF on the risk of cardiovascular death was 3 times greater in women than in men (HR 2.9) [2].

Similarly, a US Medicare beneficiaries' study has shown that the ischemic stroke risk among women with AF was progressively higher with advancing age. Despite lower incidence/prevalence of AF compared with men, ischemic stroke rates are consistently higher in women. A pathobiological rationale for the increased hazard of ischemic stroke in women remains elusive; various explanations including hormonal factors and hemodynamic differences between sexes have been

postulated. A supplementary analysis of the Medicare study data identified a significantly higher thromboembolic (CHADS) score for women regardless of age, providing a plausible explanation for higher ischemic stroke rates among women relative to men.

Acknowledging all this data AF should probably be treated more rigorously in women. In general studies show that the ischemic stroke rate decreased markedly in all age categories comparing data from 1992 and 2010 which was attributed mainly to the use of anticoagulant therapy. Namely, warfarin use increased from 15 % to 49 %. Using a large population-based cohort from Quebec, Avgil Tsadok and associates found that although the hazard of stroke was 14 % higher in women than in men, prescription warfarin use was similar for both. This observation led to lack of confidence in the effectiveness of warfarin in reducing stroke among elderly women with AF and to conjecture and debate as to whether newer anticoagulants may be more effective [3].

US Medicare beneficiaries study identified higher warfarin use among men than among women in each age category studied, especially in the most elderly subgroups [3]. Various clinical factors could contribute to lower warfarin use rates among women, such as higher prevalence of clinical contraindications or higher perceived risk of bleeding complications. This area deserves further investigation. Nevertheless, women with AF are less likely to receive anticoagulants despite their higher risk of stroke compared with men.

A meta-analysis of randomized clinical trials that reported on major bleeding and stroke with DOACs in women and men with AF included more than 66 000 patients and only 37,8 % were women. Women treated with DOACs were at higher risk of stroke and systemic embolism compared with men (RR = 1.19) but there was a significantly lower risk of major bleeding in women compared with men (RR = 0.86) [4]. According to the conclusions of the meta-analysis DOAC use should probably be sex specific and encouraged even more in women with AF than in men.

Pharmacokinetics, pharmacodynamics, and clinical differences between sexes regarding the effect of drugs should also be taken into consideration. Women with AF have a higher risk for adverse events (1.5 - to 1.7 - fold). Warfarin dosage is strongly sex-specific, with women requiring less milligram per week than men, the older women requiring the lowest doses. There are limited data regarding sex differences in the direct oral anticoagulants (DOAC) trials, although 40 % of the patients were women. There were no significant interactions by sex regarding outcome or safety in these trials [5].

Atrial fibrillation affects more women than men and its effects on the risk of stroke and cardiovascular death are much more relevant in women. Nevertheless, women with AF are significantly less likely to receive anticoagulant treatment although the beneficial effect of warfarin and DOACs seems to be more pronounced in women.

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