Risk for a major bleed was higher for women than men receiving warfarin in patients with atrial fibrillation

Humphries KH, Kerr CR, Connolly SJ, et al. **New-onset atrial fibrillation. Sex differences in presentation, treatment, and outcome.** Circulation. 2001 May 15;103:2365-70.

QUESTION

In patients with new-onset atrial fibrillation (AF), what are the sex differences in presentation, treatment, and outcome?

DESIGN

Inception cohort followed for 3 years.

SETTING

6 cities across Canada.

PATIENTS

899 patients (mean age 62 y, 62% men) with a first diagnosis of AF confirmed by electrocardiography (ECG). Exclusion criteria were flutter or fibrillation resulting from intracardiac catheter insertion or removal, life-threatening illness, or inability to give informed consent or report for follow-up.

ASSESSMENT OF PROGNOSTIC FACTORS

Data were collected at enrollment on symptoms, clinical and laboratory variables, medical history, ECG and echocardiographic data, medication history, and therapeutic interventions. Additional data were collected during follow-up on AF recurrence, medication use, therapeutic interventions, and clinical history. Association between sex and prognostic factors was assessed using univariate and multivariate analyses.

MAIN OUTCOME MEASURES

Progression to chronic AF, recurrence of paroxysmal AF, myocardial infarction, stroke, major bleed, and death.

MAIN RESULTS

On presentation, women were older than men ($P < 0.001$), were more likely to seek medical advice because of symptoms ($P < 0.001$), and experienced higher heart rates during AF ($P = 0.001$). Use of antithrombotic medications did not vary by sex. However, women ≥ 75 years of age were less likely than older men to receive warfarin but twice as likely to receive acetylsalicylic acid. More men than women (20% vs 13%, $P = 0.039$) had electrical cardioversion, but the treatment was equally successful in both sexes. The recurrence rate of AF was higher in women than in men ($P < 0.05$). Cumulative incidence of chronic AF at 3 years was identical in men and women (19%). Incidence of stroke, myocardial infarction, major bleeds, and death did not vary by sex, but women on warfarin were 3.4 times more likely than men on warfarin to have a major bleed.

CONCLUSIONS

Women with new-onset atrial fibrillation present at an older age and, compared with older men, are more often treated with aspirin than warfarin. When treated with warfarin, women have a higher incidence of major bleeds than men.

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COMMENTARY

Several trials have clearly shown the value of thromboprophylaxis in AF; the risk for stroke is not uniform, and risk stratification can target high-risk groups who would particularly benefit from warfarin (1).

The prospective observational study by Humphries and colleagues identifies important sex differences in AF, particularly with regard to thromboprophylaxis. Older women (> 75 y) were less likely than older men to receive warfarin and more likely to receive aspirin, despite older women being at high risk. Among patients receiving warfarin therapy, women were 3.4 times more likely to have a major bleed than were men. The reasons for this are unclear: The women had more hypertension and hyperthyroidism, but perhaps clinically important sex differences in hemostatic and fibrinolytic processes, which seem to play a role in AF, also exist (2). The reported incidence of major bleeds for women on warfarin, 9.2% over 3 years, is based on just 10 events but appears to be higher than the rates reported elsewhere in clinical trials and observational studies of warfarin therapy. The mean international normalized ratio (INR) for women who experienced bleeds was 4.02, markedly above the recommended INR range of 2 to 3. Thus, poor INR control may also be responsible for the excess bleeding.

The safety and efficacy profiles of warfarin and aspirin in the older age group, especially in women, need to be addressed in ongoing studies. The weight of current evidence still suggests that appropriate use of warfarin in AF, based on published guidelines using clinical and echocardiographic risk stratification (1) and ensuring tight INR control, can reduce the substantial mortality and morbidity associated with stroke without an excess of hemorrhagic complications.

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