EDITORIAL COMMENT

Gender-Related Differences in Atrial Fibrillation*

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Gender-related differences in coronary artery disease have been long recognized (1,2). There are distinct differences in clinical presentation, outcome, and intensity of investigation and therapy. Less emphasis had previously been directed towards gender differences in arrhythmias, although it has long been known that women have a higher mean heart rate and a longer QT interval (3). Differences in outcomes between men and women have been well described in the LQTS Registry (4,5).

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In all age groups, men have a higher incidence of atrial fibrillation than women. However, because the incidence of atrial fibrillation increases dramatically with age and because there are more women in the population older than the age of 75 years, the absolute number of women and men with atrial fibrillation in this age group is equal (6–9). In general, women present at an age approximately five years older than men. This difference is analogous to the later presentation of coronary artery disease in women. Women are more symptomatic than men, possibly because of faster heart rates and small body habitus (9,10). In the Canadian Registry of Atrial Fibrillation (CARAF), women experienced a significantly increased frequency of symptomatic recurrences, although there was no difference in electrocardiographically documented occurrences (9).

Studies also have demonstrated differences in the clinical characteristics. The CARAF investigators demonstrated that, at the time of initial presentation of atrial fibrillation, men have a higher burden of ischemic heart disease whereas women have a higher prevalence of hypertension and a history of thyroid dysfunction (9). The Framingham study cohort suggested that there were higher incidences of congestive heart failure, valvular heart disease, and diabetes (6). Although women have a lower incidence of atrial fibrillation, some studies have demonstrated a worse outcome and a higher rate of recurrence after cardioversion (11,12).

Differences in treatment patterns and drug-induced adverse events also have been described. Several studies have reported the underuse of anticoagulation in women older than the age of 75, a subgroup with a particularly high risk of thromboembolic events (9,13). However, the CARAF investigators have found that women were 3.35 times more likely to experience a major bleed than men (9). Thus, anticoagulation requires particularly careful monitoring in women. Proarrhythmia due to antiarrhythmic drugs (particularly torsade de pointes induced by sotalol) is considerably higher in women than in men and may adversely affect the outcomes (14).

In this issue of the Journal, Rienstra et al. (10) provide an important new insight into gender differences in the management of atrial fibrillation. Using data from the Rate Control versus Electrical Cardioversion (RACE) study, the authors found no difference between cardiovascular morbidity and mortality between women and men, but women who were randomized to the rhythm control strategy were at significantly increased risk of the primary composite end point of death from cardiovascular cause, heart failure, thromboembolic complications, bleeding, adverse affects from antiarrhythmic drugs, and pacemaker implantation compared with women who were randomized to rate control. This end point occurred in 11% of women assigned to the rate control arm and 33% of those assigned to the rhythm control arm. Significant differences were observed in four of the components of the composite end point: death from cardiovascular cause, heart failure, thromboembolic complications, and adverse affects from antiarrhythmic drugs. There were no differences in outcomes between the rate control versus rhythm control arms in men.

In addition to this important novel finding, the results of this study were consistent with the findings from other studies in that the women affected were older, had a higher symptom load, had a poorer quality of life, and had an increased prevalence of hypertension and diabetes. Men had a higher prevalence of coronary artery disease and previous myocardial infarction.

This study has important implications. The RACE study and others have demonstrated that there is no advantage to overall survival between a rate or rhythm control strategy (15–17). However, these studies all had elderly populations and, because both rate and rhythm control strategies had to be acceptable alternatives, patient characteristics favored a relatively asymptomatic group. There remains a need for rhythm control in many patients, particularly a younger active population with a high symptomatic burden. One alternative is pacemaker implantation and atrioventricular node ablation, but this strategy usually is recommended after failure of or intolerance to antiarrhythmic drugs. Thus, the higher symptom burden in women with atrial fibrillation may force an increased emphasis on rhythm control.

This study tells us that care must be undertaken in managing women with a rhythm control strategy. The
largest absolute difference in end points between women in the rate and rhythm control strategies occurred because of adverse effects attributed to antiarrhythmic drugs, including bradycardia and proarrhythmic effects. Women are well known to have an increased propensity to drug-induced torsade de points, particularly with sotalol (14,18). In general, particular care should be given to elderly women and to those with renal dysfunction. In patients with significant structural heart disease, hospitalization is recommended for initiation of sotalol and other antiarrhythmic drugs except amiodarone.

In this study, there was not an increased incidence of bleeding in women compared with men, an observation that has been observed in other studies. This study has reinforced the fact that bleeds occur predominantly in patients with high international normalized ratio (INR) levels. Other studies used more population-based, “real-world” patient populations (9,13) whereas, in this closely regulated study, INR control may have been more rigid. Anticoagulation clinics, which are common in the Netherlands where this study was conducted, also may lead to better control. Women in a community setting may be more prone to variable INR control and may be more prone to bleeding. Thus, women may have a higher risk of bleeding in a general population setting, suggesting increased vigilance should be given to maintain therapeutic INR levels.

An interesting finding is the lack of difference between rate and rhythm control strategies with respect to quality of life. Quality of life in women with atrial fibrillation remains lower than men and lower than control women in both arms of this study. A possible explanation is that the sensitivity and side effects from antiarrhythmic drugs in the rhythm control arm may offset the high symptomatic burden of palpitations and fatigue seen in the rate control arm.

Because of the decreased quality of life in women compared with men, regardless of treatment strategy, a curative, catheter-based procedure for atrial fibrillation appears very attractive. The rapidly evolving techniques and technology and the expansion of indications to include individuals with persistent and permanent atrial fibrillation in normal and abnormal hearts, might be particularly useful to improve the quality of life in women. One study has demonstrated that women are referred later after presentation for ablation of supraventricular tachycardia (19). However, gender-related differences in referral patterns and outcomes for ablation of atrial fibrillation have not been evaluated.

In summary, the current study should alert us to potential differences in treatment strategies for women versus men with atrial fibrillation. Specifically, caution should be exercised with the administration of antiarrhythmic drugs and the use of rate control or nonpharmacologic rhythm control should be considered. Further studies are required to assess relative outcomes of curative ablation procedures between men and women.

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