Sex Effect in Atrial Fibrillation
Is It All About Atrial Function?

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Over the past 25 years, our knowledge concerning embolic stroke, secondary to atrial fibrillation, has increased exponentially. Although it is well accepted that atrial fibrillation increases the risk of stroke in aggregate in a population ≈5-fold, several risk score models exist to further predict who will benefit from stroke prophylaxis with anticoagulants. The $CHADS_2$ risk score had been the standard in assessing risk in any individual patient with atrial fibrillation for several years. More recently, the $CHADS_2VASC$ score has become favored by more recent guidelines as the recommended algorithm to guide oral anticoagulant decisions.[1,2] This risk model importantly includes female sex as an important risk factor in stroke secondary to atrial fibrillation. This inclusion of female sex as a risk factor was formed on the basis of multiple studies.

See Article by Yoshida et al

Fang et al studied sex differences in over 13 000 patients[3] in the ATRIA study (Anticoagulation and Risk Factors in Atrial Fibrillation). His group found almost double the risk of stroke in women compared with men when off warfarin. In studying over 5000 patients taking part in the Euro Heart Survey, Dagres et al[4] also found that women had almost twice the risk of stroke. However, in this study, the risk was highest when female sex was in addition to at least one further traditional risk factor. Since development of the CHA_2DS_2VASc, a plethora of larger studies have confirmed the importance of sex in risk of cardioembolic stroke in atrial fibrillation. The Swedish Atrial Fibrillation Cohort Study looked at over 180 000 patients and showed a hazard ratio of 1.4 for risk of stroke in atrial fibrillation.[5] This was similar to the hazard ratio for vascular disease. Friberg looked at over 100 000 patients with atrial fibrillation and without oral anticoagulant, finding women had a 47% higher risk of stroke. When adjusted for more risk factors in the female group, women still had almost 20% higher risk.[6] These studies solidified the placement of sex as a risk factor for stroke.

Furthermore, it has been noted that not only are women at greater risk of stroke but, in fact, seem to be susceptible to more severe strokes than men when they do occur.[7] In our own retrospective review of over 200 consecutive patients with atrial fibrillation and acute stroke, we found that female sex was associated with a 2-fold risk of severe disabling or fatal recurrent cardioembolic stroke.[8] Likewise, Li et al[9] reported that women were at a higher risk of more disabling stroke in the setting of atrial fibrillation. Multiple large population studies have confirmed the increased risk of stroke in women.[3–5,10] Studies indicate a prevalence of 20% to 50% higher risk in women than in men.[6]

So then what accounts for this difference observed in the female patient with atrial fibrillation? Previous hypotheses have suggested hormonal influences, including a potential thrombogenic effect of estrogen, as well increased risk secondary to treatment with hormone replacement therapy, or even more common use of antiplatelet therapy in men because of higher rates of atherosclerotic vascular disease. These theories were refuted after further careful examination of the population studied.

The article by Yoshida et al[11] in the current issue of *Circulation: Cardiovascular Imaging* offers perhaps an alternative mechanism for development of cardioemboli and the increased incidence of stroke in women. The authors examined a group of over 400 subjects to test the effective sex difference of $CHADS_2VASC$ associations with left atrial function and anatomy. When men and women were compared, the women were found to have evidence of impaired left atrial function. Furthermore, a significant association between the CHA_2DS_2VASc risk score and left atrial function as evidenced by left atrial ejection fraction was demonstrated in women only. Likewise, global peak left atrial strain showed a similar association. Despite the shortcomings of this study, such as unmatched demographics, an important hypothesis emerges; that is, women with atrial fibrillation are more likely to have impaired LA function.

It has long been noted that the presence of left atrial spontaneous contrast indicates an increased risk for stroke in patients with atrial fibrillation. In fact, the denser the spontaneous echo contrast, the higher the risk of stroke. Likewise, the presence of decreased left atrial appendage velocity in many reports of <20 cm/s indicates a high risk of subsequent cerebral ischemia in these patients. Previous studies have also indicated the relationship between left atrial size and potential for stroke in the presence of atrial fibrillation. Most of the studies were dominated by a high percentage of male patients, making it difficult to evaluate the effects of sex on these structural and functional risk factors of the left atrium.

Previous studies have in fact demonstrated a relationship between left atrial structure and stroke.[12,13] Multiple investigators have reported that factors, including left atrial size and function, as well as left atrial appendage velocities,

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are clearly associated with the development of spontaneous echo contrast, thrombus, and ultimately stroke.[14,15] We use the parameters routinely to assess stroke risk in all patients. However, none of these studies have reported an association with female sex.

The findings demonstrated by Yoshida et al, however, need to be kept in context. The relationship between depressed left atrial function and female sex was with $CHADS_2VASC$ stroke risk scoring tool. Future research efforts should be directed toward demonstrating a direct relationship between impaired left atrial function and the incidence of and severity of stroke in women.

Additionally, it is concerning that despite an overwhelming amount of evidence pointing to increased rate of stroke in women and new data showing an increased morbidity because of stroke, it seems that women with atrial fibrillation remain under anticoagulation compared with male counterparts.[16–19] The differences were significant at ≈5% less for women across the studies. Impressively, Shantsila et al[19] found that just <50% of women with an indication for anticoagulation were prescribed an anticoagulant.

In conclusion, the report by Yoshida provides a mechanism of LA dysfunction to explain worse outcomes in females with atrial fibrillation. Findings such as these will have direct clinical implications. Future studies are needed to confirm these findings.

Disclosures

None.

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