


When will we learn? Differential outcomes in women following catheter ablation of atrial fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia worldwide and is associated with poor quality of life and increased medical costs.¹ The prevalence of AF has been constantly on the rise with the increasing age of the population. There has been an evolution in our understanding of the pathophysiology of AF, coupled with a substantial advancement in our management strategies over the past decades. Moreover, we have identified major differences in AF pathophysiology, presentation, time to diagnosis, prognosis and outcomes between men and women. Given these differences, the scope of management of AF varies as men and women respond differently to catheter ablation and medical therapy.

In their *Heart* paper, Park *et al* examined the sex difference in outcomes of antiarrhythmic drug (AAD) therapy in patients who had recurrence of AF post-catheter ablation.² They included 2999 patients of which 26.5% were women. Compared with men, women were older ($p < 0.001$), had a lower body surface area ($p < 0.001$), lower proportions of persistent AF ($p = 0.002$), smaller left atrial (LA) dimension ($p < 0.001$) and more frequent non-pulmonary vein triggers ($p < 0.001$). Post-ablation, 1094 patients (36.5%) had recurrence of their AF of which 788 patients (72.0%) were treated with AADs. Their study showed that the risk of recurrence of AF after de novo ablation was higher in women than in men ($p = 0.04$). Additionally, AADs' response after recurrence was significantly better in women than in men ($p = 0.003$). They also showed that outcomes post-catheter ablation did not differ by age; however, patients who were older than 60 years of age had less AF recurrence after being treated with AADs ($p = 0.016$). The combined analysis of sex and age showed that women younger than 60 years of age had a higher rate of recurrence post-AF

catheter ablation ($p = 0.004$); but on the other hand, women older than 60 years of age had a more favourable outcome with better rhythm control post-AADs ($p = 0.003$).

Prior studies have also looked at the sex difference in outcomes following catheter ablation for AF. A meta-analysis by Cheng *et al*, looking at 19 observational studies that included 151 370 patients of which 34% were women, showed the rate of freedom from AF/atrial tachycardia (AT) recurrence was lower in women than men at 2.4-year follow-up (OR: 0.75, 95% CI: 0.69 to 0.81; $p < 0.0001$).³ The reasons for this difference are not clear, but one possibility is the late referral of women for catheter ablation observed previously, increasing the chance that women may have progressed to persistent AF, a situation in which rhythm strategies are less successful.⁴ Additionally, a prospective multinational study conducted by ESC-EORP European Heart Rhythm Association showed that women who are referred for AF catheter ablation are usually older (61.0 vs 56.4 years; $p < 0.001$), have more comorbidities, more severe symptoms (94.1% vs 89.7%; $p < 0.001$) and a greater number of episodes of AF per month (6.9 vs 6.2; $p < 0.001$) compared with men.⁵ Women have a higher prevalence of

non-PV triggers, which may explain the higher risk of recurrence if these triggers are not targeted during ablation.⁴ Moreover, a study by Akoum *et al* looking at percentage of late gadolinium enhancement (fibrosis) detected on specific LA MRI on LA showed that women with a history of AF have a higher percentage of atrial fibrosis and LA remodelling compared with men (figure 1), which in turn contributes to poorer outcomes with catheter ablation.⁶ In regards to AAD therapy, women are known to have a longer baseline QTc and higher risk of adverse effects with AADs including class IA and class III AADs.^{7,8} The RACE trial showed that women on AADs had a higher risk of proarrhythmia including torsade de pointes and 1:1 conduction during atrial flutter, as well as bradycardias, including sick sinus syndrome and the need for pacemaker implantation.⁸

Data regarding differential sex responses were evaluated in the randomised Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Study.⁹ CABANA randomised 2204 patients to catheter ablation or drug therapy (rhythm and or rate control medications). Women represented 37% of those enrolled. Compared with men, women were older (median age, 69 years for women vs 67 years for men), were more symptomatic (48% Canadian Cardiovascular Society AF Severity Class 3 or 4 vs 39% for men), had more symptomatic heart failure (42% with New York Heart Association Class \geq II vs 32% for men) and more often had a paroxysmal AF pattern at enrolment (50% vs 39% for men) ($p < 0.0001$ for all). Moreover, there was no difference in the

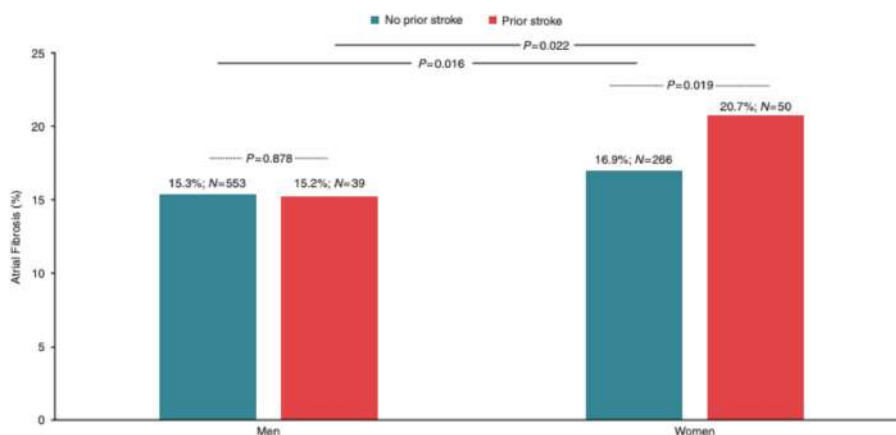


Figure 1 This figure compares the amount (%) of MRI-detected atrial fibrosis in men and women with a history of atrial fibrillation, and according to the presence or absence of prior stroke. No significant difference in atrial fibrosis was seen in men regardless of prior stroke or not. In contrast, women with a history of stroke had a significantly higher burden of atrial fibrosis when compared with women who had not had a prior stroke.⁶ Used with permission.

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primary outcome by sex (death, disabling stroke, serious bleeding or cardiac arrest; interaction $p=0.299$). AF recurrence was significantly reduced in ablation patients; however, the therapy effect was greater in men compared with women (men: HR 0.64 (95% CI 0.51 to 0.82); women: HR 0.48 (95% CI 0.40 to 0.58); interaction $p=0.060$).

The findings of Park *et al* are novel in an area that has not been well studied. However, there are several limitations to their study. The approach to AF ablation differed between patients, which may have accounted for the difference in outcomes between men and women. Women were more likely to be on amiodarone (the most effective AAD) compared with men and could have confounded the study results.

Accordingly, further analyses of randomised trials may reveal further insights. Ultimately, future randomised clinical trials should be powered to adequately assess sex-specific differences.

AF is a dynamic and complex disease process with many areas of knowledge gaps. Women have been under-represented in clinical trials with data compilation into a single analysis not accounting for the sex-specific differences. The study by Park *et al* highlights areas for future research including the sex difference of catheter ablation on LA substrate, remodelling and neurohormonal modulation, as well as how those changes interplay with the pharmacological effects of

AADs post-catheter ablation. The current data on sex hormonal effects on AF are derived primarily from animal and observational studies. Human studies would be important to better understand the effect of sex hormones on the pathophysiology of AF and its effect on treatment outcomes. This will help us develop targeted sex-specific management strategies, and perhaps future gender-directed guidelines for management of AF.

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REFERENCES

- 1 January CT, Wann LS, Calkins H, *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines and the heart rhythm Society. *J Am Coll Cardiol* 2019;74:104–32.
- 2 Park YJ, Park J-W, Yu HT, *et al*. Sex difference in atrial fibrillation recurrence after catheter ablation and antiarrhythmic drugs. *Heart* 2023;109:519–26.
- 3 Cheng X, Hu Q, Gao L, *et al*. Sex-Related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Europace* 2019;21:1509–18.
- 4 Patel D, Mohanty P, Di Biase L, *et al*. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm* 2010;7:167–72.
- 5 Grecu M, Blomström-Lundqvist C, Kautzner J, *et al*. In-Hospital and 12-month follow-up outcome from the ESC-EORP EHRA atrial fibrillation ablation long-term registry: sex differences. *Europace* 2020;22:66–73.
- 6 Akoum N, Mahnkopf C, Kholmovski EG, *et al*. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. *Europace* 2018;20:1086–92.
- 7 Hohnloser SH, Crijns HJGM, van Eickels M, *et al*. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;360:668–78.
- 8 Rienstra M, Van Veldhuisen DJ, Hagens VE, *et al*. Gender-Related differences in rhythm control treatment in persistent atrial fibrillation: data of the rate control versus electrical cardioversion (race) study. *J Am Coll Cardiol* 2005;46:1298–306.
- 9 Russo AM, Zeitler EP, Giczewska A, *et al*. Association between sex and treatment outcomes of atrial fibrillation ablation versus drug therapy: results from the CABANA trial. *Circulation* 2021;143:661–72.