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EAST-AFNET 4 Trial Investigators; Van Gelder, Isabelle C; Ekrami, Neda Khalilian; Borof, Katrin; Fetsch, Thomas; Magnussen, Christina; Mulder, Bart A; Schnabel, Renate; Wegscheider, Karl; Rienstra, Michiel

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## Letters

### Sex Differences in Early Rhythm Control of Atrial Fibrillation in the EAST-AFNET 4 Trial



Evidence is growing on sex differences in incidence, prevalence, comorbidities, and outcomes of atrial fibrillation (AF) patients.<sup>1-3</sup> Women are generally older, have more often hypertension and heart failure with preserved ejection fraction, and less often coronary artery disease. Further, women are generally more symptomatic. Despite this higher symptom load, the data suggest that women are less likely to undergo atrial ablation and more often experience antiarrhythmic drug-associated proarrhythmia. These differences in rhythm control (RC) management call for more information on the efficacy and safety of RC therapy in women with AF.

The EAST-AFNET 4 (Early Treatment of AF for Stroke Prevention Trial) demonstrated a benefit of early RC therapy for early AF patients.<sup>4</sup> The aim of this prespecified subanalysis was to assess whether there are sex differences in clinical presentation, and whether the effectiveness and safety of early RC therapy interact with sex. The protocol was approved by the ethics review boards of all institutions involved.

The primary outcome was time to a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.<sup>4</sup> The primary safety outcome was a composite of death from any cause, stroke, or prespecified serious adverse events of special interest capturing complications of rhythm-control

therapy. For the first primary outcome proportional hazards models with an interaction term of treatment group and sex as well as site as a shared frailty term were used. The treatment effect is presented as the incidence rate ratio and 95% CI.

Of all patients included, 1,293 (46.4%) were women, 645 randomized to early RC and 648 to usual care. Women were older (mean age  $71 \pm 8$  years; men  $70 \pm 8$  years;  $P < 0.001$ ), more often had sinus rhythm at baseline (women 750 [58%]; men 755 [51%];  $P < 0.001$ ), and were less often asymptomatic (women 300 [25%]; men 501 [36%];  $P < 0.001$ ). CHA<sub>2</sub>DS<sub>2</sub>-VASc score was higher in women (women  $3.7 \pm 1.33$ ; men  $3.0 \pm 1.19$ ;  $P < 0.001$ ), with slightly different distribution of the components of concomitant conditions. Women and men received similar types of initial early RC (antiarrhythmic drug 88.0% and 86.0%, ablation 8.1% and 8.0%, in women and men, respectively;  $P = 0.82$ ). At 2 years, in the early RC group, 416 of 589 (70.6%) women and 483 of 693 (69.7%) men were still receiving RC therapy ( $P = 0.903$ ). In the usual care group, 481 of 530 (91%) women and 584 of 641 (91%) men were still not receiving RC therapy ( $P = 0.401$ ). Therapy of concomitant cardiovascular conditions was well balanced without differences between sexes or randomized groups.

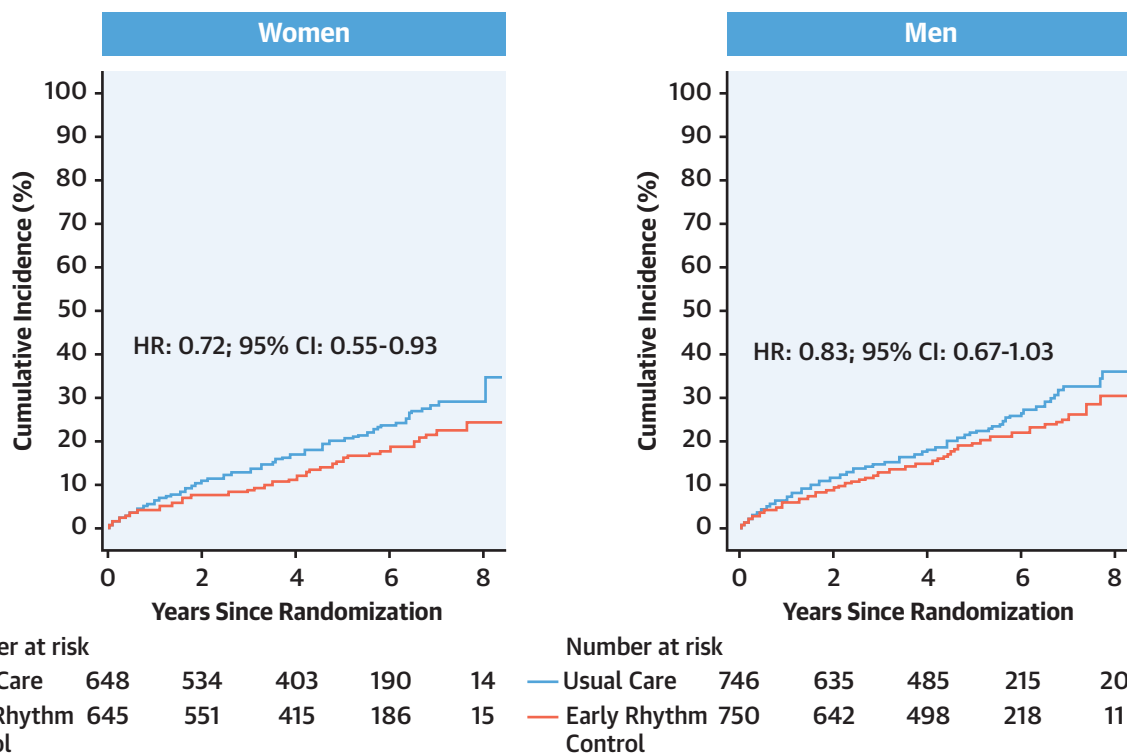
After a median of 5.1 years, a first primary-outcome event occurred in 100 women assigned to RC (3.4 per 100 patient-years), and 137 women assigned to usual care (4.7 per 100 patient-years) (HR: 0.72; 95% CI: 0.55-0.93), and in 149 men assigned to early RC vs 179 men assigned to usual care (4.3 vs 5.2 per 100 patient-years in men, respectively) (HR: 0.83; 95% CI: 0.67-1.03) (Figure 1). There was no difference in treatment effect of early RC between sexes ( $P$  interaction = 0.408). The primary safety outcome was also comparable (women: early RC 102 of 645 [15.8%], usual care 94 of 648 [14.5%]; men: early RC 129 of 750 [17.2%]; usual care 129 of 746 [17.3%]). Serious adverse events related to RC were rare in both sexes. Sinus rhythm at 2 years was comparable (women: early RC 428 of 506 [84.6%], usual care 333 of 511 [65.2%]; men: early RC 493 of 616 [80.0%]; usual care 354 of 624 [56.7%];  $P$  interaction = 0.746). Symptoms improved to a similar extent in women and men.

#### What is the clinical question being addressed?

Is the benefit of early RC similar in women and men with recently detected AF?

#### What is the main finding?

Early RC improves cardiovascular outcomes in patients of either sex without differences in safety.

**FIGURE 1** Cumulative Incidence Curves of Primary Outcome in Women and Men

Aalen-Johansen cumulative incidence curves of the first primary outcome in women and men defined as time to a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome. The curves show no difference in reduction of cardiovascular outcomes with early rhythm control therapy between women and men with early atrial fibrillation and cardiovascular conditions. *P* interaction = 0.408. No adjustments for multiplicity were applied.

Thus, in this prespecified subanalysis of the EAST-AFNET 4 trial, we show that a strategy of initiating RC in both women and men with early AF and concomitant cardiovascular conditions was associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for heart failure or acute coronary syndrome compared with usual care during 5 years of follow-up. Safety of early RC was similar between women and men.

\*Isabelle C. Van Gelder, MD, PhD  
Neda Khalilian Ekrami, MD  
Katrin Borof, MSc  
Thomas Fetsch, MD  
Christina Magnussen, MD  
Bart A. Mulder, MD, PhD  
Renate Schnabel, MD, PhD  
Karl Wegscheider, MSc  
Michiel Rienstra, MD, PhD

Paulus Kirchhof, MD, PhD  
for the EAST-AFNET 4 Trial Investigators

\*Department of Cardiology  
University of Groningen  
University Medical Centre Groningen  
P.O. Box 30.001  
9700 RB Groningen, the Netherlands  
E-mail: [i.c.van.gelder@umcg.nl](mailto:i.c.van.gelder@umcg.nl)  
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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