Arrhythmic Risk in Male and Female Patients With Heart Failure—Same but Different
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Risk prediction for sudden cardiac death (SCD) is challenging, and the use of left ventricular ejection fraction, with all its shortcomings, remains the mainstay for risk stratification and indication for the implantation of primary prevention implantable cardioverter-defibrillators (ICDs) in patients with heart failure. Despite ICDs' widespread use, most recipients will never receive an ICD shock.

Women have a lower overall risk of succumbing to cardiovascular disease than men, yet sex-specific analyses of all landmark randomized controlled trials for the prevention of SCD by primary prevention ICD implantation have been hampered by the low overall number of women enrolled.

Saxena and colleagues from the Multicenter Automatic Defibrillator Implantation Trial (MADIT) study group help to fill this gap by reporting the sex-specific outcomes in the aggregate data of 4 landmark primary prevention ICD trials. Their cohort study retrospectively analyzed the data of 4506 patients, 1075 (24%) thereof being women. They showed that women had a 40% lower risk of first and recurrent ventricular tachyarrhythmic (VTA) events during a 3-year follow-up compared with men. The all-cause mortality was unusually low, at 9%, and not different between women and men. The risk of VTA was still significantly higher than the competing risk of nonarrhythmic mortality, but less pronounced in women.

The study in part corroborates the findings of a large retrospective European cohort of 5000 patients with primary prevention ICD implantation, which demonstrated that female ICD recipients received fewer appropriate ICD shocks (hazard ratio [HR], 0.61; 95% CI, 0.47-0.79), but also had lower all-cause mortality (HR, 0.65; 95% CI, 0.53-0.79). One of the proposed reasons for this sex difference was the higher proportion of female patients with nonischemic cardiomyopathy. Saxena et al demonstrate that although the risk reduction for VTA was reduced to a greater extent in patients with nonischemic cardiomyopathy (HR, 0.50; 95% CI, 0.38-0.66), it also could be observed in patients with ischemic cardiomyopathy (HR, 0.73; 95% CI, 0.56-0.95) (P = .03 for interaction). This indicates that other sex-specific differences must play a role.

Several observations deserve comment. First, the authors chose sustained VTA, defined as ICD-recorded VT greater than 170 beats/min or ventricular fibrillation, as their primary end point. According to the results of the MADIT-RIT study, this very slow VT-monitor or intervention zone does not reflect contemporary ICD programming, and this end point does not equal prevented SCD. Appropriate shock therapy in the ventricular fibrillation zone is the best surrogate for prevented SCD and, indeed, the authors could demonstrate a significantly lower appropriate shock rate for women.

Second, the interpretation of the data is also complicated by the fact that half of the women and a third of the men also received very effective heart failure therapy in the form of a cardiac resynchronization ICD (CRTD). The use of CRT along with an ICD in only some patients already made the interpretation of the DANISH trial complex, in which no survival benefit by the use of a primary prevention ICD could be observed in a population with nonischemic heart failure. In the MADIT cohort, significantly more women received a CRTD. However, the authors could not find a difference in the reduction of the primary end point in women between those who received only an ICD and those who carried a CRTD.

Third, the etiology of heart failure was different, with most men having ischemic cardiomyopathy (74%), whereas most women had nonischemic cardiomyopathy (42%). Patients
with post–myocardial infarction have an ischemic transmural or endocardial scar as the arrhythmic substrate, whereas nonischemic cardiomyopathy constitutes a variety, with pathologies from postmyocarditis to infiltrative diseases, such as sarcoid, or genetically determined causes, such as laminopathies. Although the overall mortality is lower in nonischemic cardiomyopathy, the individual risk may be very different, depending on the underlying pathology.

How can the presented results be helpful in daily decision-making? It is unlikely that the specificity and negative predictive value of a single risk parameter (eg, clinical, derived from an electrocardiogram or magnetic resonance imaging) will suffice to replace left ventricular ejection fraction as a risk marker in primary prevention. Composite risk scores such as the MADIT-ICD benefit score or the DERIVATE score are more likely to be of benefit. Sex-specific risk stratification will undoubtedly play an increasing role in the quest to provide patients at highest risk for SCD with costly defibrillator therapy. The work by Saxena et al underlines once more that there are important differences in cardiovascular outcomes between men and women and that the underrepresentation of women in randomized controlled trials is a problem that needs to be taken into account.

**ARTICLE INFORMATION**

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**REFERENCES**


