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Commentary

Sex differences in ICDs for primary prevention: Time to include women in ICD trials!

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Although half of patients with cardiovascular disease are women, women have been underrepresented in randomized controlled trials in cardiology for too many years (average representation 38.2%) [1], with even lower representation in implantable cardioverter defibrillator (ICD) trials for primary prevention (ranging from 8.2% of patients in the Multicenter Automatic Defibrillator Implantation Trial - MADIT-I trial to 28.8% in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation - DEFINITE). Therefore, guideline recommendations and clinical care are based on research conducted mostly in men. The risks and benefits of ICD implantation for primary prevention in patients with heart failure with low ejection fraction (HFrEF) presents an excellent case for demonstrating the problems with not adequately including women in cardiology trials. At present, ICD is recommended for patients with HFrEF (<35%) without any differentiation by sex [2]. However, there is reasonable evidence suggesting that ICDs may be of smaller, if any, benefit in women [3,4]. In a recent metanalysis of all major RCT evaluating ICD for primary prevention ICD implantation was not associated with improved survival in female patients compared with optimal medical therapy alone (HR = 0.93, 95% CI 0.68–1.27) [4]. The limited benefit of the ICD for primary prevention in women was already suggested by previous meta-analyses before the publication of the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure (DANISH trial) (HR = 1.01, 95% CI: 0.76–1.33) [3]. This lack of benefit is particularly concerning given the fact that women have higher degree of device related complications after implantation [5]. However, well-intentioned, are we offering a treatment and exposing women to a procedure with higher risk of complications without clear evidence of benefit?

A potential physiologic explanation for the lack of ICD benefit in women is the fact that, in general, they have lower susceptibility to ventricular arrhythmia, are less vulnerable to sudden death and have higher prevalence of non-ischemic cardiomyopathy compared with men [6–8]. The reason why women are less susceptible to ventricular tachycardia (VT) is still unclear however this is likely a multifactorial process due to hormonal differences in channel expression in the myocardium leading to different patterns of cardiac repolarization, different autonomic response to stress, degree of vagal activation and difference is lifestyle and risk factors exposure.

Additionally, data supporting ICD for primary prevention in HF are from trials published between late 1990s and early 2000s. However, undoubtedly treatment for HF has significantly evolved since those trials, including new classes of medication (SGLT2) and cardiac resynchronization therapy (CRT). In fact, women are usually better responders to CRT than men [9], likely due to higher prevalence of non-ischemic cardiomyopathy [10]. This gender difference is important because responders to CRT are also at lower risk for VT [11]. Data shows that in primary prevention patients with CRT indication, the addition of a defibrillator might convey additional benefit only in well-selected male patients [7].

In this issue, Han et al., have done an elegant review of the data on ICD implantation in women [12]. The authors highlighted that most of the data questioning the benefit of ICD implantation in women are from sub analysis of RCT, metanalysis of RCT and observational trials and thus should be considered mainly as hypothesis generating data. However, it is disappointing to note, that since the publication of MADIT-1 in 1996, little effort has been made to include woman in RCTs for ICD for

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primary prevention and guideline recommendations have been unchanged despite the lack of significant data in women. The AnaLysIs of Both sex and device specific factoRs on outcomes in pAtients with non-ischemic cardiomyopathy (BIO-LIBRA) [13] has been designed with the primary goal to understand with if there are differences in treatment response based on the patient's sex (pre-specified minimum of 40% female participants). Unfortunately, the observational nature of the trial and the lack of control subjects make it unable to answer the question of whether ICDs offer any benefit in women compared to medical therapy. Thus, until better data has been generated, it remains unclear if women have any benefit with ICD implantation for primary prevention, especially in the new area of therapy for heart failure.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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