Do Women Benefit Equally as Men from the Primary Prevention Implantable Cardioverter-Defibrillator?

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Women traditionally have been and are still underrepresented in research in many important areas of cardiology. Accordingly, guideline recommendations, which also encompass women, are mostly based on research conducted predominantly in men. A clear example of issues arising from inter-gender extrapolation of data occurs with the existing guidelines for the primary prevention implantable cardioverter-defibrillator (ICD); however this issue has received scarce attention so far[1].

Currently, the ICD is broadly indicated for primary prevention of sudden cardiac death (SCD) in heart failure patients with low ejection fraction (≤30-35%), without any differentiation by sex[1]. This is largely based on evidence from four major randomized controlled trials: *Sudden Cardiac Death in Heart Failure Trial* (SCD-HeFT), *Multicenter Automatic Defibrillator Implantation Trial II* (MADIT-II), *Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation* (DEFINITE) and, to a lesser extent, *Multicenter Unsustained Tachycardia trial* (MUSTT). In addition, the *Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure* (COMPANION) trial has shown the benefit of cardiac resynchronization therapy (CRT), with or without an ICD, as compared to optimal medical therapy. However, as is often the case with other areas of research in cardiology, women have been significantly under-represented in ICD trials (ranging from 9.7% of patients in the MUSTT trial to 28.8% in DEFINITE).

There is plausible cause to believe that sex may have a potential influence on the benefit derived from the ICD, alone or in association with CRT. Firstly, women are at a substantially lower risk of all-cause death compared to men, with the SCD-HeFT trial showing that placebo treated women have a lower 5-year mortality than ICD treated men[2]. Secondly, there is evidence to suggest that women are less prone to develop life-threatening ventricular arrhythmias and SCD compared to men[3,4], and SCD occurs later in

life on average[4]. Thirdly, women have been described as having a higher likelihood of response to CRT compared to men[5]. Thus, in the setting of concomitant CRT, this higher response rate in women may further reduce their risk of ventricular arrhythmias and SCD. Our recent large multicentre study in the context of CRT and primary prevention has shown that the addition of a defibrillator might convey additional benefit only in well-selected male patients[6]. This is likely the result of the low risk of SCD among women in general regardless of the presence of the defibrillator, especially in the context of non-ischaemic dilated cardiomyopathy.

We assessed the possible relationship between sex and outcome with ICD implantation in the setting of primary prevention, by pooling the results of MUSTT, MADIT-II, DEFINITE, COMPANION, SCD-HeFT and DANISH trials in a meta-analysis (**table 1**). Since the first MADIT study had the inducibility of ventricular tachycardia despite intravenous procainamide as an inclusion criterion, which currently has limited applicability in clinical practice, we opted not to include it in the present analysis. Likewise, the DINAMIT and IRIS trials were not included as ICD implantation is not currently recommended early after an acute myocardial infarction. We pooled results for female and male patients separately. Random-effects models were used given the known heterogeneity in the design of the included trials. Hazard ratios (HR) were used as a measurement of treatment effect and pairwise comparisons were performed for the primary endpoint of total all-cause mortality. A supplementary analysis was performed to assess the individual contribution of each study to the pooled estimate by recalculating the pooled HR after excluding that particular study. Statistical heterogeneity was quantified using the I^2 statistic. All statistical analyses were carried out using the Comprehensive Meta-analysis v3 software.

The design of selected trials and baseline data are summarized in **table 1**. As expected, female patients represented a minority in all of the trials, ranging from 9.7% of patients in the MUSTT trial to 28.8% in DEFINITE or 32.2% in COMPANION. Two studies included patients with ischaemic cardiomyopathy only (MUSTT and MADIT-II), whereas DEFINITE and DANISH focused on patients with non-ischaemic cardiomyopathy. SCD-HeFT and COMPANION included both ischaemic and non-ischaemic patients. Cardiac resynchronization therapy was used in both the COMPANION and DANISH trials. According to the Delphi Consensus criteria for randomized controlled trials, study quality was high since all studies had a clearly stated method of randomization, similar baseline groups with respect to the most important prognostic predictors, intention-to-treat analyses, independent committees for adjudication of events and point estimates and measures of variability consistently provided for the primary outcome measures.

Overall, 5,356 male patients (2,377 receiving ICD vs. 2,979 on optimal medical therapy [OMT] alone) followed-up for approximately 17,270 patient-years and 1,578 female patients (735 ICD vs 843 OMT alone) with a follow-up of approximately 5,231 patient-years were included. The pooled data revealed that, in men, the presence of the ICD was associated with lower mortality risk compared with OMT alone (HR=0.75, 95%CI 0.67-0.84; p<0.001; I^2=11%) **[Figure 1].** When excluding the CRT-D vs. OMT comparison of the COMPANION trial, a significant reduction in mortality was still seen in the ICD group (pooled HR=0.76, 95%CI 0.67-0.86; p<0.001) **[Figure 2]**. In contrast with the findings observed among men, the ICD was not associated with improved survival in female patients compared with OMT alone in the pooled analysis (HR=0.93, 95%CI 0.68-1.27; p=0.63; I^2=36%) **[Figure 1].** After removing data from the COMPANION trial, the pooled HR was 1.01 (95%CI 0.73-1.39, p=0.96) **[Figure 2]**.

The aforementioned results suggest that, in the specific setting of primary prevention, women as a group do not seem to obtain a significant survival benefit from the ICD, contrary to men. This in turn may also have contributed to a relative underestimation of the ICD benefit among males when looking at the results in total. The limited benefit of the ICD for primary prevention in women had already been suggested by previous meta-analyses before the publication of the DANISH trial[7,8].

All of the main trials supporting the use of primary prevention ICDs were published in the late 1990s and early 2000s, with patients randomized 15 to 26 years ago. The benefit of the ICD was consistently seen in all of those trials. However, it is hardly disputable that the treatment and outcome of heart failure patients as seen in daily clinical practice have changed over the last quarter of a century. Indeed, background medical and CRT device therapy have improved over the time-course of ICD randomized studies: e.g. **i)** beta-blocker usage increasing from 69-70% in the MADIT-II and SCD-HeFT trials to 92% in DANISH; **ii)** CRT usage in 58% of DANISH patients vs. no CRT in MADIT-II or SCD-HeFT. Cardiac resynchronization therapy has been shown to reduce the risk of SCD even in the absence of the ICD[9]. Henceforth, it is unclear whether the magnitude of the benefit of the ICD has changed since the publication of MADIT-II or SCD-HeFT. The recently published DANISH trial has provided a more up-to-date estimate of the value of the ICD in non-ischaemic patients. This study suggested that non-ischaemic patients as a group do not benefit from the ICD, although a younger cohort may still derive some benefit. Although some authors have proposed that the relative mortality-reduction effect size of the primary prevention ICD has remained relatively consistent over time regardless of etiology[10], the lower overall event rate seen in the DANISH trial translated into a lower absolute mortality-reduction effect size and a significantly higher number needed to treat. Importantly, their sub-group analysis

based on sex did not show any benefit or trend for benefit in women (HR=1.03, p=0.92), a similar finding to that of the SCD-HeFT and DEFINITE trials.

There is reasonable evidence suggesting that ICDs may be of smaller benefit in women. Women in general have a lower susceptibility to ventricular arrhythmia compared with men and are less vulnerable to sudden death[3,5,11]. Furthermore, fewer of their deaths are sudden, irrespective of heart failure severity[5,12]. Although the fact that women have a higher prevalence of non-ischaemic cardiomyopathy may explain some of this variability, their lower arrhythmic risk is seen regardless of the presence/absence of coronary artery disease[9]. The underlying causes for the less aggressive arrhythmic profile of women are unclear. Several mechanisms have been proposed: hormonal differences affecting arrhythmic vulnerability, different autonomic response to stress, degree of vagal activation, differences in cardiac repolarization, genetic variants influencing adrenergic receptors, adherence to a low-risk lifestyle, and nutritional, behavioral and psychological factors. It is also noteworthy that women are in general better responders to CRT than men[4]. Responders and super-responders to CRT are at lower risk of ventricular arrhythmias[13]. Two recent meta-analyses revealed that **i)** the potential benefit of the ICD in CRT studies decreases with increasing percentage of female patients[14], and **ii)** the risk of SCD amongst patients with CRT-pacemaker decreases with increasing percentage of female patients[15]. In a large multicentre cohort study of primary prevention CRT patients, we have shown that the addition of a defibrillator might convey additional benefit only in well-selected male patients[5]. The potential lack of benefit of the ICD in female CRT patients was likely a result of their much lower risk of SCD (especially in those with non-ischaemic dilated cardiomyopathy)[5]. In fact, amongst women with a biventricular pacemaker, only 2.2% of the

excess unadjusted mortality compared with those receiving CRT-Defibrillator was related to sudden cardiac death[5].

Subgroup analyses should never be over-interpreted, as true causality can only be unequivocally assessed through a randomized controlled trial. However, though the presented meta-analysis, based on subgroup analyses, should be considered mainly hypothesis-generating, our findings should call for further research to specifically clarify the role of ICDs in women. It is now time for the medical and research communities to actively question the presumed overarching benefit of ICDs irrespective of sex and engage in systematic scientific efforts to definitively evaluate the value of this intervention in women.

REFERENCES

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *Europace.* 2015 Nov;17(11):1601-87.

2. Russo AM, Poole JE, Mark DB, Anderson J, Hellkamp AS, Lee KL et al. Primary prevention with defibrillator therapy in women: results from the Sudden Cardiac Death in Heart Failure Trial. *J Cardiovasc Electrophysiol* 2008;19:720–4.

3. Kannel WB, Wilson PW, D'Agostino RB CJ. Sudden coronary death in women. *Am Hear J* . 1998;136:205–12.

4. Bogle B, Ning H, Mehrotra S, Goldberger J, Lloyd-Jones M. Lifetime Risk for Sudden Cardiac Death in the Community. *J Am Heart Assoc.* 2016 Jul; 5(7): e002398.

5. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I et al; MADIT-CRT Executive Committee. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol* 2011;57:813–20.

6. Barra S, Providência R, Duehmke R, Boveda S, Marijon E, Reitan C et al; French-UK-Sweden CRT Network. Sex-specific outcomes with addition of defibrillation to resynchronisation therapy in patients with heart failure. *Heart.* 2017 Jan 19. pii: heartjnl-2016-310677. doi: 10.1136/heartjnl-2016-310677. [Epub ahead of print]

7. Ghanbari H, Dalloul G, Hasan R, Daccarett M, Saba S, David S et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;169:1500–6.

8. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart.* 2015 Nov;101(22):1800-6.

9. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;27:1928–32.

10. Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. *Eur Heart J.* 2017 Feb 21. doi: 10.1093/eurheartj/ehx028.

11. MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P et al. Sex Differences in Implantable Cardioverter-Defibrillator Outcomes: Findings From a Prospective Defibrillator Database. *Ann Intern Med*; 2012;156:195.

12. Rho RW, Patton KK, Poole JE, Cleland JG, Shadman R, Anand I et al. Important differences in mode of death between men and women with heart failure who would qualify for a primary prevention implantable cardioverter-defibrillator. *Circulation* 2012;126:2402–2407.

13. Ruwald MH, Solomon SD, Foster E, Kutyifa V, Ruwald A-C, Sherazi S et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy. *Circulation* 2014;130:2278–86.

14. Barra S, Providência R, Tang A, Heck P, Virdee M, Agarwal S. Importance of Implantable Cardioverter-Defibrillator Back-Up in Cardiac Resynchronization Therapy Recipients: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2015 Nov 6;4(11).

15. Barra S, Providencia R, Duehmke R, Boveda S, Begley D, Grace A et al. Cause-of-death analysis in patients with cardiac resynchronization therapy with or without a defibrillator: a systematic review and proportional meta-analysis. *Europace.* (In press)

FIGURE LEGENDS

Figure 1: Forest plots comparing ICD vs. optimal medical therapy (OMT) alone according to sex (endpoint: all-cause mortality)

Figure 2: Forest plots comparing ICD vs. optimal medical therapy (OMT) alone regarding all-cause mortality after exclusion of individual studies

TABLE 1 - Selected studies for the meta-analysis

Study name	Year	Study design	Sample size (number of patients)					Follow-up (months)	Age	Female sex	Ischaemic etiology	LV ejection fraction (mean)	NYHA class III/IV	Previous NSVT	Previous AF	CRT
			Total		ICD	OMT	Total									
MUSTT	1999	Multi-centre, RCT	704	**Men**	145	491	636	39	66.5	9.7%	100%	29.5%	24.5%	100%	9%	0%
				Women	16	52	68									
MADIT-II	2002	Multi-centre, RCT	1232	**Men**	623	417	1040	20	64.5	15.9%	100%	23%	28.8%	NA	8.5%	0%
				Women	119	73	192									
DEFINITE	2004	Multi-centre, RCT	458	**Men**	166	160	326	29	58.3	28.8%	0%	21.4%	21%	90.6%	24.5%	0%
				Women	63	69	132									
COMPANION*	2004	Multi-centre, RCT	903	**Men**	399	213	612	16 (ICD) 14.8 (non-ICD)	66.7	32.2%	56.3%	22%	100%	NA	0%	65.9% (all in the ICD group)
				Women	196	95	291									
SCD-HeFT	2005	Multi-centre, RCT	2521	**Men**	639	1294	1933	45.5	60.1	22.8%	52.7%	24.7%	30%	23.1%	15.2%	0%
				Women	190	398	588									
DANISH	2016	Multi-centre, RCT	1116	**Men**	405	404	809	67.6	63.5	27.5%	0%	25%	46.5%	NA	13.3%	58%
				Women	151	156	307									

Legends: CRT- Cardiac resynchronization therapy; LV- Left ventricular; NA- Not available; NYHA- New York Heart Association

*Comparison was made between patients receiving cardiac resynchronization therapy defibrillator vs. optimal medical therapy alone