Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: A systematic review and meta-analysis

Pasquale Santangeli, MD,* Gemma Pelargonio, MD, PhD,* Antonio Dello Russo, MD, PhD,* Michela Casella, MD, PhD,* Caterina Bisceglia, MD,* Stefano Bartoletti, MD,* Pietro Santarelli, MD,* Luigi Di Biase, MD,*‡¶ Andrea Natale, MD, FHRS†¶

*From the *Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy, †Department of Biomedical Engineering, University of Texas, Austin, Texas, ‡Department of Cardiology, University of Foggia, Foggia, Italy, and ¶Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas.*

BACKGROUND Women are underrepresented in primary prevention implantable cardioverter-defibrillator (ICD) trials, and data on the benefit of ICD therapy in this subgroup are controversial.

OBJECTIVE The purpose of this study was to better evaluate the benefit of prophylactic ICD in women by performing a meta-analysis of primary prevention ICD trials that assessed gender differences on the end-points of total mortality, appropriate ICD intervention, and survival benefit of ICD compared with placebo.

METHODS PubMed, CENTRAL, and other databases were searched in October 2009. Studies were included only if they examined gender differences in the specified end-points, providing the hazard ratio (HR) obtained in multiple Cox regression analyses, and adjusted for all confounding variables.

RESULTS We retrieved five studies (MADIT-II, MUSTT, SCD-HeFT, DEFINITE, COMPANION) that enrolled 7,229 patients (22% women) with dilated cardiomyopathy (74% ischemic). Compared to men, women had no significant difference in overall mortality (HR 0.96, 95% confidence interval [CI] 0.67–1.39, $P = .84$) but experienced significantly less appropriate ICD interventions (HR 0.63, 95% CI 0.49–0.82, $P \leq .001$). The benefit of ICD on mortality was significantly higher in men (HR 0.67, 95% CI 0.58–0.78, $P < .001$) but did not reach statistical significance in women (HR 0.78, 95% CI 0.57–1.05, $P = .1$).

CONCLUSION Women enrolled in primary prevention ICD trials have the same mortality compared to men while experiencing significantly less appropriate ICD interventions, thus suggesting a smaller impact of sudden cardiac death on overall mortality in women with dilated cardiomyopathy. These findings may explain the smaller ICD survival benefit among women.

KEYWORDS Dilated cardiomyopathy; Gender differences; Implantable cardioverter-defibrillator; Sudden cardiac death

ABBREVIATIONS CI = confidence interval; **DCM** = dilated cardiomyopathy; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **LVEF** = left ventricular ejection fraction; **SCD** = Sudden cardiac death.

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Introduction

Multiple randomized clinical trials have shown primary prevention of sudden cardiac death (SCD) with an implantable cardioverter-defibrillator (ICD) in patients with left ventricular dysfunction to be effective.[1] However, the real benefit of prophylactic ICD therapy in underrepresented subgroup of patients, such as women, has not been consistently demonstrated.[2–5] In fact, studies assessing gender differences in arrhythmic risk showed conflicting results,[2–7] and no clear-cut evidence supports the same benefit of prophylactic ICD therapy in the two genders.[8]

To better evaluate the presence and possible causes of gender differences in effectiveness of prophylactic ICD therapy in patients with left ventricular dysfunction, we performed a meta-analysis of primary prevention ICD studies on the end-points of total mortality, appropriate ICD intervention, and net ICD survival benefit in women compared to men.

Methods

Searching strategy and selection process

Two trained investigators (PS, GP) independently searched major web databases for all published studies that (1) had a prospective randomized design, (2) tested ICD therapy versus placebo in patients with dilated cardiomyopathy (DCM) who did not previously experience major arrhythmic events,

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and (3) reported an estimate of the risk for specified end-points for women compared to men, adjusted for all possible baseline confounders or covariates. Citations initially selected by systematic search were first retrieved as a title and/or abstract and preliminarily screened. Potentially suitable citations were then retrieved as complete manuscripts and assessed for compliance to inclusion criteria. Detailed search strategy is given in the Appendix.

Quality assessment

Study quality was evaluated according to the established methods of the Cochrane Collaboration. Specifically, we separately estimated the risk of selection, performance, detection, and attrition bias.[9]

Study end-points

The end-points of interest were total mortality, appropriate ICD intervention, and survival benefit of ICD therapy compared to placebo. Appropriate ICD intervention was defined as intervention on rapid sustained ventricular tachycardia or fibrillation and was chosen as a surrogate end-point of SCD because adjusted risk estimates for SCD in the control group were not retrievable from the included studies.

Data analysis

Data from each study were entered as logarithm hazard ratio (HR) with its standard error and combined with a DerSimonian-Laird random effect inverse variance weighted method to obtain the summary estimate of the end-point, expressed as HR with 95% confidence interval (CI).[9] For pooled analyses on end-points that involved direct comparisons between women and men (i.e., total mortality and appropriate ICD therapy), we pooled the values of HR (women vs men) provided in the model of multiple Cox regression analysis in each study and adjusted for the maximum number of confounding factors and covariates in order to provide estimates that may be minimally affected by baseline differences between the two genders.

With regard to the pooled analysis on the end-point of ICD survival benefit, which did not involve a direct comparison between genders but reported relative risk estimates within genders (i.e., ICD vs placebo among women and, separately, ICD vs placebo among men), we again performed a meta-regression analysis using inverse variance weighting (which weighs each study on the basis of its precision) to appraise the impact on ICD survival benefit within genders of potential confounders not considered in the original studies, such as age, etiology of DCM (i.e., ischemic vs nonischemic), New York Heart Association functional class, left ventricular ejection fraction (LVEF), nonwhite race, baseline drug therapy, and length of study follow-up.

In order to assess the sensitivity of the results, additional analyses were conducted as follows. In the absence of statistical heterogeneity, a fixed effect inverse variance weighted method was performed as well to obtain the summary estimate of the end-point. For each end-point, statistical analyses were also performed after excluding each study in turn. Analyses were conducted, excluding in turn studies enrolling ischemic DCM patients only (MADIT-II [Multicenter Automatic Defibrillator Implantation Trial-II], MUSTT [Multicenter Unsustained Tachycardia Trial]), studies that mixed ischemic with nonischemic DCM patients (SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial], COMPANION [Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure]), and the study that enrolled nonischemic DCM patients only (DEFINITE [Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation]).

The presence of heterogeneity among studies was evaluated with Cochrane Q Chi-square test, and inconsistency was assessed with I^2 test, which describes the percentage of variability in effect estimates that is due to heterogeneity. I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high, respectively.[10] Publication bias was assessed using the asymmetry linear regression of the Egger test and visually as funnel plot of precision against treatment effect.

The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUORUM) guidelines.[11] Statistical level of significance was defined at two-tailed $P < .05$. Analyses were performed using Review Manager 5.0 (The Cochrane Collaboration) and STATA 10.1 (Stata Corporation, College Station, TX, USA) packages.

Results

Search results and study selection

The search permitted retrieval of 3,467 citations. We identified nine eligible citations, which were assessed according to compliance to the inclusion criteria. Among the retrieved but excluded studies, DINAMIT (Defibrillator in Acute Myocardial Infarction Trial)[12] and IRIS (Immediate Risk Stratification Improves Survival)[13] did not provide adjusted estimates of the risk of total mortality and appropriate ICD therapy in women compared to men and thus did not meet inclusion criteria.

Ultimately, five published studies (MADIT-II, MUSTT, SCD-HeFT, DEFINITE, COMPANION)[2–5,14] were selected and included in the meta-analysis (Figure 1 and Table 1).

Pooled analysis of the end-point of total mortality was conducted on four studies (MUSTT, MADIT-II, SCD-HeFT, DEFINITE);[2–5] the adjusted estimate of the risk of mortality in women compared to men was not available for COMPANION.[15,16] Moreover, because the design of MUSTT was different from that of other studies, with patients allocated to different treatment arms according to the results of electrophysiologic test,[17] we considered patients noninducible at the electrophysiologic test to be more consistent with the other study patients and thus eligible for final pooled analysis on the end-point of total mortality.[4,17] However, for sensitivity analyses, we included also patients of both the electrophysiologically guided and the no electrophysiologically guided therapy groups.[4]

Pooled analysis of the end-point of appropriate ICD therapies was conducted on four studies (MADIT-II, SCD-

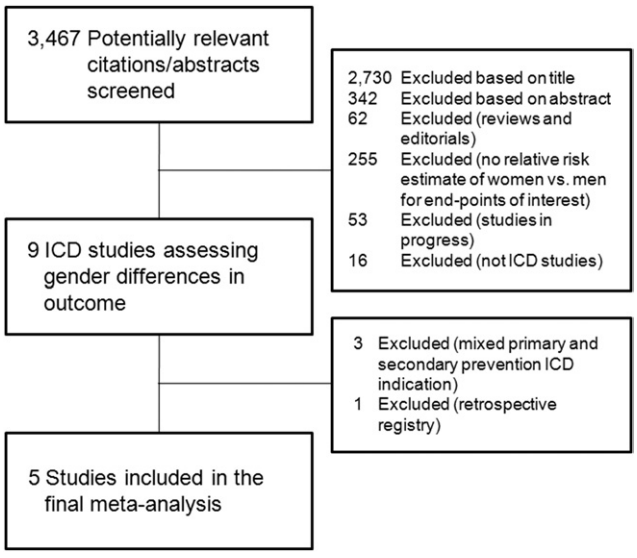

Figure 1 Selection process of studies included in the meta-analysis.

HeFT, DEFINITE, COMPANION);[2,3,5,15] in the MUSTT study, only a minority of patients in the electrophysiologically guided therapy group (46%) actually received an ICD, and no estimate of the risk of this end-point (women vs men) was available. Sensitivity analyses for this end-point were conducted, including data on the arrhythmic events of the electrophysiologically guided therapy group of the MUSTT study[4] and excluding data from the COMPANION study.[14,15]

Pooled analysis on the end-point of ICD survival benefit compared to placebo was conducted on four studies (MADIT-II, SCD-HeFT, DEFINITE, COMPANION).[14,16,18,19] Baseline clinical characteristics of women and men were available in four studies (MUSTT, MADIT-II, DEFINITE, SCD-HeFT).[2–5]

Baseline characteristics

Table 1 lists the baseline characteristics of the five studies included in the final analyses. All studies were multicenter trials. The five studies included a total of 7,229 patients with DCM, of whom 5,340 (74%) had an ischemic etiology and 1,630 (23%) were women. A nonwhite race was more prevalent in women compared to men in all the included studies. Women tended to have more advanced disease than men, with a higher prevalence of New York Heart Association functional class greater than II (36% vs 28%, respectively, in SCD-HeFT)[3] and left bundle-branch block (25% vs 17%, respectively, in MADIT-II),[5] and more use of diuretics (Table 2).

Women received less renin-angiotensin system blockers and were less likely to have previous coronary revascularization procedures in the two studies enrolling only patients with ischemic DCM (MADIT-II, MUSTT).[4,5]

Mean LVEF was 24% and was not different between women and men among all included studies, with the exception of MUSTT,[4] in which a higher proportion of men had LVEF <30% (51% vs 44%, P = .046; Table 2). Follow-up duration ranged from 24[17,19] to 60[16,18] months (mean follow-up 41 ± 18 months).

Quantitative data synthesis: Total mortality

Considering the end-point of total mortality, women had the same overall mortality as men (HR = 0.96, 95% CI 0.67–1.39, P = .84, I^2 = 80%; Figure 2A). Similar results were obtained with fixed-effect estimates of HR (HR = 0.90, 95% CI 0.79–1.04, P = .16, I^2 = 80%). Sensitivity analysis for total mortality showed results similar in direction and statistical significance. In particular, exclusion of the noninducible registry patients of MUSTT and inclusion of either the electrophysiologically guided or no electrophysiologically guided therapy group of MUSTT[4] yielded the same estimate results (HR = 0.84, 95% CI 0.62–1.14, P = .26; and HR = 0.81, 95% CI 0.60–1.10, P = .18, respectively). The results were not affected by all the prespecified sensitivity analyses. Thus, these data support our findings despite the evident extent of clinical and statistical heterogeneity.

Publication bias was not detected by either visual estimation or Egger test (bias 1.44, 95% CI –12.17 to 15.07, P = .69).

Quantitative data synthesis: Appropriate ICD intervention

Pooled analysis of the end-point of appropriate ICD intervention showed a significantly lower rate of appropriate ICD intervention in women compared to men (HR = 0.63, 95% CI 0.49–0.82, P <.001, I^2 = 0%; Figure 2B). A

Table 1 Characteristics of the included studies

Study (reference no.)	Year	No. of patients	No. (%) of women	Clinical scenario of DCM patients	Follow-up (months)
MUSTT[4,7]	1999	1,498*	223 (16%)*	LVEF ≤40%, prior MI, NSVT	39
MADIT-II[5,19]	2002	1,232	192 (16%)	LVEF ≤30%, prior MI	20
DEFINITE[2,18]	2004	458	132 (29%)	LVEF ≤35%, nonischemic, PVCs or NSVT	29
SCD-HeFT[3,16]	2005	2,521	588 (23%)	LVEF ≤35%, prior MI and nonischemic	45
COMPANION[14,15]	2004	1,520	493 (32%)	LVEF ≤35%, prior MI and nonischemic	16

Follow-up represents median value in MUSTT, COMPANION, and SCD-HeFT and mean value in the MADIT-II and DEFINITE.

DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSVT = nonsustained ventricular tachycardia; PVCs = premature ventricular complexes.

*Noninducible registry patients.

Table 2 Baseline characteristics of men and women in the included studies

	MUSTT[4]		MADIT-II[5]		DEFINITE[2]		SCD-HeFT[3]	
	Men (n = 1,265)	Women (n = 233)	Men (n = 1,040)	Women (n = 192)	Men (n = 326)	Women (n = 132)	Men (n = 1,933)	Women (n = 588)
Age (years) [mean ± SD, median (range), or n (%) <70]	835 (66)	156 (67)	65 ± 10	64 ± 11	57.9	59.1	60 (52–69)	60 (50–67)
Nonwhite race	177 (14)	56 (24)**	110 (11)	49 (25)**	94 (29)	55 (42)**	406 (21)	182 (31)**
New York Heart Association functional class >II	NR	NR	643 (63)	132 (70)	65 (20)	31 (24)	541 (28)	212 (36)
Ischemic etiology	1,265 (100)	233 (100)	1,040 (100)	192 (100)	0 (0)	0 (0)	1,102 (57)	200 (34)**
Nonischemic etiology	0 (0)	0 (0)	0 (0)	0 (0)	326 (100)	132 (100)	831 (43)	388 (66)**
LVEF (%) [mean ± SD, median (range), or n (%) <30%]	645 (51)	103 (44)*	23.1 ± 5.4	23.6 ± 5.7	21 (7–35)	22 (10–35)	24 (20–30)	25 (20–30)
Prior revascularization†	949 (75)	149 (64)**	626 (60)	81 (42)**	0 (0)	0 (0)	1,411 (73)	394 (67)
ECG parameters								
Atrial fibrillation	114 (9)	19 (8)	96 (9)	9 (5)*	NR	NR	329 (17)	53 (9)**
Left bundle branch block	63 (5)	26 (11)**	164 (17)	45 (25)*	NR	NR	NR	NR
Medication								
Angiotensin converting enzyme inhibitor	911 (72)	177 (76)	822 (79)	136 (71)*	310 (95)	124 (94)	1,662 (86)	476 (81)*
Beta-blocker	455 (36)	70 (30)	655 (63)	113 (59)	277 (85)	112 (85)	1,334 (69)	400 (68)
Diuretics‡	721 (57)	154 (66)*	759 (73)	163 (85)**	NR	NR	1,565 (81)	506 (86)*
Digoxin	696 (55)	147 (63)*	603 (58)	123 (64)	140 (43)	51 (39)	1,314 (68)	435 (74)

Values are expressed as n (%).

LVEF = left ventricular ejection fraction; NR = not reported.

†Percutaneous or surgical coronary revascularization in MUSTT and SCD-HeFT, surgical coronary revascularization in MADIT-II.

‡Loop diuretics in SCD-HeFT. In the other studies, type of diuretic used was not specified.

*$P \leq .05$, **$P \leq .001$ for comparisons between men and women.

fixed-effect estimate of HR yielded the same results due to the absence of statistical heterogeneity for this end-point. Sensitivity analyses showed results similar in direction and statistical significance. Point estimates and 95% CIs for HRs all remained <1.0 when performing all the prespecified sensitivity analyses. Moreover, inclusion of data from the arrhythmic events of the electrophysiologically guided therapy group of MUSTT[4] and exclusion of data from COMPANION[14] in order to obtain a pool of studies consistent with that of the end-point of total mortality did not change the results (HR = 0.68, 95% CI 0.51–0.90, $P = .007$).

Publication bias was not detected by either visual estimation or Egger test (bias –2.51, 95% CI –6.70 to 1.68, $P = .12$).

Quantitative data synthesis: ICD survival benefit and meta-regression analysis on ICD survival benefit

Among men, ICD therapy was associated with a significant 33% reduction of total mortality compared to the placebo arm (HR = 0.67, 95% CI 0.58–0.78, $P < .001$, $I^2 = 0\%$; Figure 3A). On the other hand, prophylactic ICD therapy in women was associated with a smaller and nonsignificant reduction of mortality (HR 0.78, 95% CI 0.57–1.05, $P = .1$, $I^2 = 0\%$; Figure 3B). The results were not different after validity assessment with additional sensitivity analyses. In particular, exclusion of COMPANION[14] did not affect the significant ICD survival benefit among men (HR = 0.67,

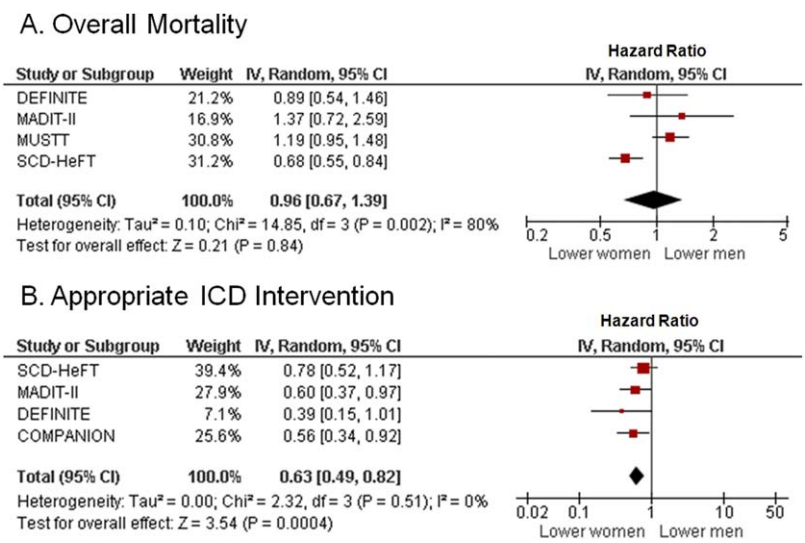

Figure 2 Forest plot showing adjusted hazard ratio of overall mortality (whole study population) **(A)** and appropriate implantable cardioverter-defibrillator (ICD) intervention **(B)** in women compared to men in each study and the overall adjusted hazard ratio. *Square boxes* denote hazard ratio; *horizontal lines* represent 95% confidence interval (CI).

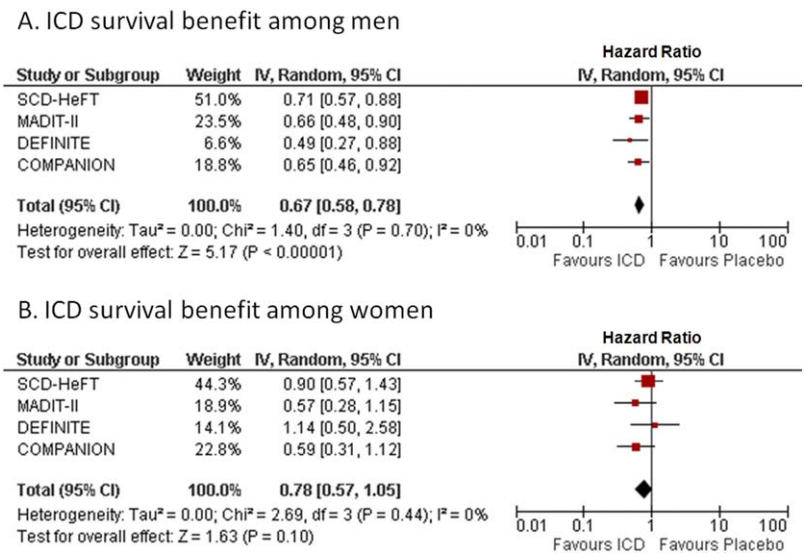

Figure 3 Forest plot showing hazard ratio of survival benefit associated with implantable cardioverter-defibrillator (ICD) use in women (**A**) and in men (**B**) in each study and the overall hazard ratio. *Square boxes* denote hazard ratio; *horizontal lines* represent 95% confidence interval (CI). In SCD-HeFT, placebo denotes the no-amiodarone group; in COMPANION, placebo denotes the standard medical therapy group (no cardiac resynchronization therapy).

95% CI 0.57–0.80, $P < .001$) or the nonsignificant benefit among women (HR = 0.84, 95% CI 0.59–1.19, $P = .33$).

In order to evaluate the potential confounding effect of clinical and study characteristics on the pooled estimate of ICD survival benefit within genders, a meta-regression analysis was performed. Meta-regression analysis failed to disclose significant interactions between the variables of interest and outcome (Table 3).

Discussion

This systematic review was designed to assess gender differences in outcome after prophylactic ICD placement and is based on the statistical pooling of five randomized studies, which enrolled more than 7,200 patients, and specifically compared women with men with regard to clinical outcome.

Table 3 Effect of clinical and study characteristics on pooled mortality reduction estimate (hazard ratio) with prophylactic implantable cardioverter-defibrillator therapy in the two genders as assessed by meta-regression analysis

	Men		Women	
Variable	Beta	*P* value	Beta	*P* value
Age	0.364	.5	−0.126	.4
Ischemic dilated cardiomyopathy	0.001	.4	−0.006	.4
New York Heart Association functional class	0.005	.5	−0.014	.4
Left ventricular ejection fraction	0.133	.4	−0.052	.8
Nonwhite race	−0.015	.4	0.038	.4
Angiotensin-converting enzyme inhibitor	−0.018	.4	0.030	.4
Beta-blocker	−0.014	.4	0.025	.4
Follow-up duration	0.002	.9	0.012	.6

With more than 1,600 women, this meta-analysis includes the largest women cohort to date and shows that women enrolled in primary prevention ICD trials have the same overall mortality as compared to men, while experiencing significantly less appropriate ICD interventions and a nonsignificant survival benefit from ICD therapy.

Significant findings and clinical implications

Our results support the concept that SCD has a smaller impact on total mortality in women with DCM and severe left ventricular dysfunction and suggest a smaller survival benefit of prophylactic ICD therapy in this subgroup of patients.

The clinical implications of the findings are potentially very significant. Despite the impressive increase in ICD insertion in the last years, event rates for SCD have not equally decreased.[20] On the other hand, the systematic implementation of current LVEF-based prophylactic ICD recommendations has resulted in a substantial number of ICD placements without any clinical benefit.[21]

Disturbingly, these issues are even more puzzling among women, who have been largely underrepresented in ICD trials.[16–19] Our results further put in perspective current ejection fraction-based ICD recommendations,[1] raising concern about the appropriateness of generalizing such recommendations to patients underrepresented in guideline-concluding trials, such as women.

Potential mechanisms

Although the underlying pathophysiology and risk factors for SCD in women are generally assumed to be similar to those in men, the limited amount of data available suggests that differences may exist. In the Framingham cohort of 2,873 women followed over a period of 38 years, Kannel et al[22] reported that women who present with SCD are less likely than men to have a history of heart disease (37% vs

56%). These findings have been supported by other studies, which consistently found a lower prevalence of coronary artery disease and left ventricular dysfunction in women than in men.[23] Thus, pathologic substrates underlying SCD seem to differ between women and men, possibly explaining the differences in the incidence of sustained ventricular arrhythmias between women and men reported in several studies. Gender differences have been noted in the inducibility of ventricular arrhythmias among patients with coronary artery disease[4] and in the frequency of nonsustained ventricular tachycardia in patients with congestive heart failure,[24] suggesting that men may have a greater propensity for ventricular arrhythmia. Accordingly, the rate of SCD is higher in men than in women,[22] and even among patients who already have an ICD implanted, women seem to experience less arrhythmic episodes than men, although different studies showed conflicting results.[25,26]

In agreement with these data, our meta-analysis found a striking lower rate of malignant arrhythmia occurrence in women than in men, without differences in overall mortality, thus suggesting significant gender differences in arrhythmic risk associated with severe left ventricular dysfunction. Moreover, because ICD therapy can only affect mortality by preventing death due to malignant arrhythmias, our data provide a mechanistic explanation for the smaller and nonsignificant survival benefit associated with prophylactic ICD therapy in women.

Validity of the meta-analysis

As with any meta-analysis, there are inherent difficulties in using data from multiple studies of a similar nature to derive definitive conclusions, especially for *post hoc* analyses.[2–5,15] On the other hand, adequate *post hoc* analyses of randomized trials, together with data from registries, represent the only opportunity to appropriately address the relevant issue of gender differences in ICD therapy benefit.

In order to provide estimates that may be minimally affected by baseline clinical differences between the two genders, we excluded from this review data from ICD registries because of the intrinsic greater difficulty in adjusting observed results for all significant baseline clinical differences and confounders.

Accordingly, a strength of our analysis is the pooling of adjusted estimates derived from multivariable Cox regression analyses, and the degree of adjustment in each study appeared optimal. Indeed, the risk of pooling crude estimates of risk may lead to misleading conclusions when dealing with gender differences in outcome. An analysis by Ghanbari et al,[8] which was conducted only on the end-point of survival benefit associated with prophylactic ICD therapy, concluded that ICD therapy does not reduce mortality in women. However, their analysis did not take into account significant baseline differences between genders, with women presenting with symptoms later and being significantly less treated for heart disease than men.

With regard to the end-point of total mortality, substantial statistical inconsistency was detected, which highlights the presence of significant differences between the included studies without, however, questioning the validity of our statistical analysis performed using a random effect pooling.

The two most recent studies in this analysis (DEFINITE, SCD-HeFT) have important differences in study design and length of follow-up and, not surprisingly, show results slightly discordant from the other studies (MUSTT, MADIT-II). DEFINITE[18] randomized only patients with nonischemic DCM, whereas SCD-HeFT[16] included a large cohort of mixed ischemic and nonischemic DCM, with a significantly higher rate of nonischemic DCM among women. These differences may explain the statistical heterogeneity on the end-point of total mortality as nonischemic DCM has consistently been reported to have a better survival than ischemic DCM.[16]

As a surrogate end-point of SCD, we considered appropriate ICD interventions in the ICD group. The reliability of appropriate ICD intervention as a "SCD equivalent" has been questioned because subsequent analysis of ICD randomized trials has shown that the number of appropriate ICD interventions exceeds the sudden death rate in the control group.[21] Although possibly overestimating the actual rate of SCD in both groups, our pooled analysis strongly supports a significant difference in ventricular arrhythmia occurrence between women and men enrolled in primary prevention ICD studies. Furthermore, this finding was consistent among all the included studies, as supported by the absence of statistical heterogeneity ($I^2 = 0\%$).

Finally, we found a smaller and nonsignificant ICD survival benefit in women compared to men, which was consistent among all the included studies ($I^2 = 0\%$) and may have potential explanation from our meta-analysis. Moreover, these results are in line with those of Ghanbari et al[8] and seem not to be influenced by gender-specific baseline clinical characteristics, as shown by the results of our meta-regression.

However, the results of the meta-regression should be viewed as hypothesis-generating only, and lack of statistical significance should not be interpreted as lack of effect, given the well-known limitations in statistical power of meta-regression. On the other side, different lengths of follow-up of included studies,[27] the presence of more advanced heart failure syndromes, and higher prevalence of nonwhite races[28] and nonischemic DCM[16,18] in women all may significantly affect overall mortality, gender-specific arrhythmic risk, and net ICD survival benefit.

Finally, the pooled HR for ICD survival benefit in women had wide confidence limits, which actually reflects their underrepresentation in ICD studies and suggests that such studies may be underpowered to show a significant benefit of ICD therapy in women. The underrepresentation of women in the primary studies may also affect the significance level of the pooled HR obtained in our meta-analysis, which therefore may be underpowered to show a statistically significant benefit of prophylactic ICD therapy. On the other hand, it should be emphasized that a study aiming to have 80% power to detect HR for mortality of 0.78 associ-

ated with prophylactic ICD therapy in patients with severe left ventricular dysfunction (alpha level 0.05) would need to randomize an overall number of 2,124 women with at least 2 years of follow-up. Such a trial enrolling a large sample of only women and randomly withholding prophylactic ICD therapy is very unlikely to be feasible. Moreover, it should be also considered that the abovementioned hypothesis would be associated with a number needed to treat with ICD of 20, which is a rather unfavorable cost-effectiveness.

Conclusion

This review presents a meta-analysis of data from five primary prevention randomized ICD studies that assessed gender differences in outcome and shows a smaller impact of SCD on overall mortality in women, which may explain their smaller and nonsignificant survival benefit from prophylactic ICD therapy.

Our findings challenge current LVEF-based prophylactic ICD recommendations, raising concerns about the appropriateness of generalizing such recommendations to subgroups of patients underrepresented in primary prevention ICD trials, and call for further studies, with appropriate economic and social analyses, to determine the cost-effectiveness of this therapy in women.

Appendix

Search strategy

The investigators independently searched PubMed, CENTRAL, BioMedCentral, Cardiosource, clinicaltrials.gov, and ISI Web of Science using highly sensitive and specific strategies. Search keywords included "randomized," "implantable cardioverter defibrillator," "ICD," "defibrillator," "sudden cardiac death," "ventricular arrhythmias," "sudden death," "dilated cardiomyopathy," "ejection fraction," "ischemic cardiomyopathy," "nonischemic cardiomyopathy," "cardiomyopathy," and "cardiomyopath*" (where * denotes a wildcard). Searches were updated to October 2009. No language restriction was used. Proceedings from the annual American Heart Association, American College of Cardiology, European Society of Cardiology, Heart Rhythm, and Europace meetings for the past 5 years were also manually searched. Websites of the American College of Cardiology, American Heart Association, and European Society Cardiology were also screened for oral presentations and/or expert slide presentations.

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