

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

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Background: Numerous clinical trials have established a role for implantable cardioverter-defibrillators in the prevention of sudden cardiac death in patients with heart failure. However, questions remain that regard the clinical benefit of these therapies in different patient subgroups. Specifically, the role of implantable cardioverter-defibrillators in women with heart failure for the primary prevention of sudden cardiac death has not been well established. Our objective is to determine whether implantable cardioverter-defibrillators reduce mortality in women with advanced heart failure.

Methods: We searched MEDLINE (1950-2008), EMBASE (1988-2008, week 24), the Cochrane Controlled Trials Register (third quarter, 2008), the National Institute of Health ClinicalTrials.gov database, the Food and Drug Administration Web site, and various reports presented at scientific meetings (1994-2007). Eligible studies were randomized controlled trials of implantable cardioverter/defibrillators for the primary prevention of sudden cardiac death in patients with heart

failure that reported all-cause mortality as an outcome for the female population. Of the 2619 reports identified, 5 trials that enroll 934 women were included in the meta-analysis.

Results: Pooled data from the 5 trials revealed no statistically significant decrease in all-cause mortality in women with heart failure who receive implantable cardioverter-defibrillators (hazard ratio, 1.01; 95% confidence interval, 0.76-1.33).

Conclusions: Implantable cardioverter-defibrillator therapy for the primary prevention of sudden cardiac death in women does not reduce all-cause mortality. Further studies are needed to investigate the reasons for this observation and to define the population of women who may benefit most from implantable cardioverter-defibrillator therapy.

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THE BURDEN OF HEART FAILURE in the United States is overwhelming. Heart failure affects approximately 5.3 million people, with women comprising nearly half that population.¹ The annual incidence of heart failure is approximately 10 per 1000 patients 65 years and older, with men and women affected in equal numbers.² In patients diagnosed as having heart failure, sudden cardiac death (SCD) occurs at 6 to 9 times the

70% of women younger than 65 years with heart failure dying within 8 years of diagnosis.^{1,2} Heart failure represents a significant public health problem, with a significant cost burden to the US health care system of approximately \$35 billion.¹ Treatment of heart failure includes optimization of medical therapy in addition to primary prevention of SCD with implantation of an implantable cardioverter-defibrillator (ICD) in those patients with reduced left ventricular ejection fraction (LVEF). This approach to the primary prevention of SCD in patients with heart failure is the result of multiple clinical trials that evaluated the efficacy of ICDs in this population. This approach has led to a significant increase in the rate of ICD implantations and is associated with an estimated \$50 000 to \$90 000 per life-year saved during 12 to 20 years.^{3,4}

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rate of the general population.^{1,2} Despite enormous progress in treatment, heart failure mortality rates remain unacceptably high, with approximately 80% of men and

However, in the absence of a significant quality-adjusted life-year benefit, the 3-year incremental cost-effectiveness ratio may be higher than \$235 000 per quality-adjusted life-year with a 95% confidence interval.⁵ Although the recommended treatment approach is widely accepted on the basis of multiple clinical trials, most patients studied have been male. Despite this inequality among the sexes, both men and women currently receive the same treatment. However, it is unclear whether female patients receive the same treatment benefit compared with male patients. Our study sought to evaluate the effectiveness of ICDs for the primary prevention of SCD in women with heart failure and reduced LVEF.

METHODS

SEARCH STRATEGY

We searched MEDLINE (1950-2008), EMBASE (1988-2008, week 24), the Cochrane Controlled Trials Register (third quarter, 2008), the National Institutes of Health ClinicalTrials.gov database of clinical trials, and the Food and Drug Administration Web site (<http://www.fda.gov>). We performed searches using the Web-based search engine Ovid with the “explode” option for each subject term and the option “AND” for combining keywords. The MEDLINE database was searched from January 1950 to week 4 of September 2008. The Medical Subject Heading terms included *defibrillators*, *implantable*; *heart failure*; and *randomized controlled trial*. We also used a previously developed MEDLINE search strategy⁶ to retrieve the strongest scientific studies of treatment by conducting a sensitive search. The EMBASE database was searched from January 1988 to week 24 of 2008 with the keywords *defibrillator*, *heart failure*, and *controlled trial*. The Cochrane Controlled Trials Register was searched with a similar approach. All searches were performed in September 2008. To identify studies reported only at scientific meetings, we performed hand searches or electronic searches of the annual scientific sessions of the American College of Cardiology (1994-2008), the American Heart Association (1994-2008), the European Society of Cardiology (1994-2008), and the North American Society of Pacing and Electrophysiology/Heart Rhythm Society (1994-2008). We conducted additional searches using 18 author names and 9 trial acronyms frequently cited in narrative reviews of cardioverter-defibrillator ICDs, as well as modified versions of the Cochrane Optimal Search Strategy for randomized trials.⁷ The bibliographies of the 33 most recent narrative review articles were also hand searched. To reduce bias, we did not restrict our searches to any specific language.⁸

STUDY SELECTION

Reports of randomized controlled trials of ICDs for the primary prevention of SCD in patients with heart failure and reduced LVEF were eligible for inclusion in the meta-analysis. *Randomized controlled trial* was defined according to the National Library of Medicine. We included trials if they reported all-cause mortality for the female population as a primary or secondary outcome. We excluded articles that described only research design or that had incomplete data. Because of the effects of cardiac resynchronization on ventricular arrhythmias and all-cause mortality, we included data derived from trials that used only ICDs. This was done to minimize variability in the assessment of this outcome. We did not exclude reports in formats other than that of a journal article.

QUALITY ASSESSMENT AND DATA ABSTRACTION

Two independent reviewers (H.G. and G.D.) evaluated the studies for inclusion in the meta-analysis. Disagreements between reviewers were resolved by a third masked reviewer (C.M.). The reviewers were masked to the authors, journal, and institution where each study was conducted. Abstracted data included eligibility criteria, baseline characteristics, medical treatment in the control arm, ICD device type and manufacturer, sponsorship, duration of follow-up, rates of crossover, handling of dropouts and withdrawals, outcomes for men and women, availability of intent-to-treat analysis, presence of an independent events committee, number of women in the trial, and cause of heart failure. Outcome of interest included all-cause mortality for women. We used a modified Jadad scale⁹ to evaluate the quality of the randomized controlled trials.

STATISTICAL ANALYSIS

Hazard ratio (HR) was chosen as the principal measure of effect. The HR from each included trial was pooled by the use of fixed-effects and random-effects models that used weighting based on inverse variance calculated according to the methods of DerSimonian and Laird.¹⁰ The *Q* test and *I*² index were used to check for quantitative heterogeneity,¹¹ with *P* < .05 deemed statistically significant. Where no significant statistical heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by the exclusion of individual trials one at a time and recalculation of the pooled HR estimates for the remaining studies. Publication bias was assessed graphically by the use of a funnel plot and mathematically by the use of an adjusted rank-correlation test, in accordance with the method of Begg and Mazumdar.¹² Sensitivity analyses were performed to assess the importance of different statistical models. All statistical analyses were performed with Comprehensive Meta-Analysis version 2.0 (Biostat Inc, Englewood, New Jersey).

RESULTS

SEARCH RESULTS

As outlined in **Figure 1**, our search identified 9 prospective randomized controlled clinical trials of ICD implantation vs medical therapy. Four trials were excluded because they did not report an outcome of interest for women. These trials were the Cardiomyopathy Trial,¹³ the Amiodarone vs Implantable Cardioverter-Defibrillator Trial,¹⁴ the Coronary Artery Bypass Graft Patch Trial,¹⁵ and the Multicenter Automatic Defibrillator Implantation Trial (MADIT) I.¹⁶ These trials enrolled a total of 1303 patients; however, only 237 patients (18%) were female.

QUALITATIVE ANALYSIS

There were 5 primary prevention trials in our meta-analysis. These trials were the Multicenter Unsustained Tachycardia Trial (MUSTT),^{17,18} MADIT II,^{19,20} the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT),²¹ the Defibrillators in Non-Ischemic Cardiomyopathy Treat-

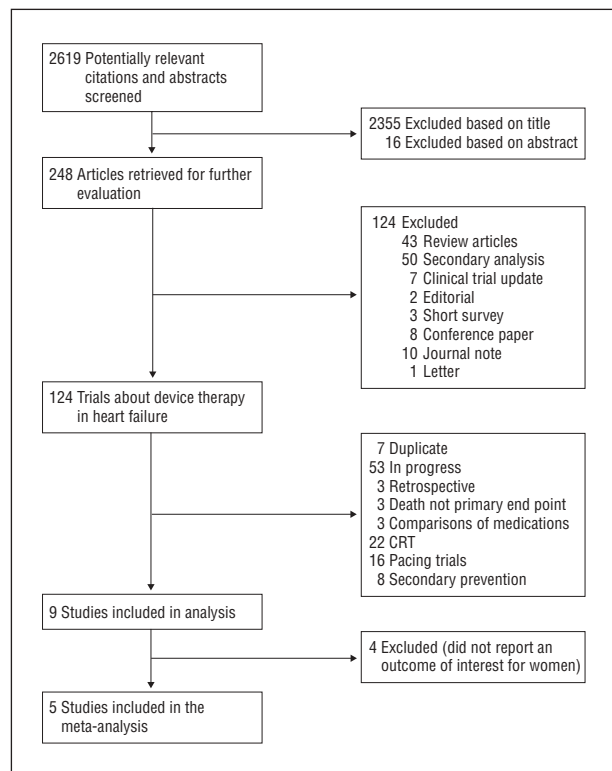


Figure 1. The Quality of Reporting of Meta-analyses flow diagram for the meta-analysis. CRT indicates chronic resynchronization therapy.

ment Evaluation (DEFINITE),^{22,23} and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).^{24,25}

There was substantial heterogeneity in the design of these trials. The DEFINITE trial randomized patients with nonischemic cardiomyopathy with an LVEF of 36% or less and ambient arrhythmia to ICD implantation or medical therapy in a 2-arm study design.²² The SCD-HeFT randomized patients with heart failure to therapy with ICD, amiodarone hydrochloride, or placebo; a total of 1676 patients were randomized to either an ICD or placebo.²⁴ MUSTT included patients with coronary artery disease and an LVEF of 40% or less and asymptomatic nonsustained ventricular tachycardia. Patients in whom sustained ventricular tachyarrhythmias were induced by programmed stimulation were randomly assigned to receive either antiarrhythmic therapy, with the inclusion of drugs and ICDs, as indicated by the results of electrophysiologic testing, or no antiarrhythmic therapy.¹⁷ We analyzed the results of MUSTT for each sex based on electrophysiologic test-guided therapy and non-electrophysiologic test-guided therapy. In DINAMIT patients who had an acute myocardial infarction with an LVEF of 35% or less and impaired cardiac autonomic function were randomized to ICD therapy vs no ICD therapy.²¹ In MADIT II, patients with a prior myocardial infarction and an LVEF of 30% or less were randomly assigned in a 3:2 ratio to receive an ICD or conventional medical therapy.

In total, our meta-analysis included data with regard to 934 women with reduced LVEF who were given therapy with ICD or a placebo in the primary prevention setting. **Table 1** summarizes the baseline characteristics

of the patients enrolled in these trials. Despite the significant heterogeneity noted in these trials, we believed that there were sufficient similarities to warrant their inclusion in the quantitative portion of our meta-analysis.

All 5 of the trials included in the analysis were of comparable quality. None of the trials reported a significant interaction between sex and ICD therapy on overall mortality. The intervention (ICD implantation) was a surgical procedure; therefore, allocation concealment and masking were not possible in these trials.²⁶ All trials used either an independent or masked committee for adjudication of events. All trials used intent-to-treat analyses and in most cases provided detailed accounting of dropouts and crossovers. Even though these trials had wide variations in crossover rates, we expected that crossovers would decrease the benefit of ICD therapy relative to medical therapy and bias the results toward a lesser benefit of ICD therapy in an intent-to-treat analysis.²⁷ **Table 2** outlines the summary measures of methodologic quality for each trial. **Table 3** summarizes the mortality rates reported for the included trials and compares the sex differences in the ICD implantation vs placebo groups. The companies whose device was the subject of study provided at least some part of the funding for each trial.

QUANTITATIVE FINDINGS

A total of 3810 men were included in our analysis. A statistically significant decrease in mortality rates was found in men with heart failure and reduced LVEF who received ICDs for the primary prevention of SCD compared with medical therapy (HR, 0.78; 95% confidence interval [CI], 0.70-0.87; $P < .001$; **Figure 2**). Minimal trial heterogeneity of the results was found ($Q = 8.25$, $P = 0.083$, $I^2 = 51.51$); hence, little difference was seen when pooled results from random-effects modeling were used.¹¹

None of the 5 primary prevention trials demonstrated a statistically significant benefit of ICD implantation over medical therapy for mortality in women. A total of 934 women from these 5 trials were included in our analysis. Pooled data analysis from the 5 selected trials did not demonstrate a statistically significant decrease in mortality in women with heart failure and reduced LVEF who received ICDs for the primary prevention of SCD compared with medical therapy (HR, 1.01; 95% CI, 0.76-1.33; $P = 0.95$; **Figure 3**). There was also minimal trial heterogeneity of the results ($Q = 5.45$, $P = 0.24$, $I^2 = 26.62$). We performed several sensitivity analyses to assess the effect of heterogeneity in trial design and patient selection on the pooled effect estimate. Exclusion of any single trial did not significantly alter the overall result of our analysis.

PUBLICATION BIAS

We assessed publication bias graphically by the use of a funnel plot of the logarithm of effect size vs the standard error for each trial and mathematically by the use of an adjusted rank-correlation test.¹² There was no evidence of significant publication bias ($P = .81$ by the Begg and Mazumdar rank-correlation test).

Table 1. Qualitative Analysis of the Studies Included in the Review

Internal Validity	DEFINITE ²²	SCD-HeFT ²⁴	DINAMIT ²¹	MUSTT ¹⁷	MADIT II ¹⁹
Follow-up, %	100	100	100 (Partial follow-up for 4 patients in the control group)	99.4	99.8
Crossover to ICD therapy, No. (%)	23/229 (10.0)	188/1692 (11.1)	0/342	46/353 (13.0)	22/490 (4.5)
Crossover to pharmacologic therapy, No. (%)	4/229 (1.7)	163/829 (19.5)	20/332 (6.0)	46/351 (13.1)	32/742 (4.3)
Intent to treat	Yes	Yes	Yes	Yes	Yes
Events committee	Yes	Yes	Yes	Yes	Yes
Jadad scale score	4	4	4	4	4
Sponsorship	St Jude Medical	NHLBI, Medtronic, Wyeth-Ayerst Laboratory, Knoll Pharmaceuticals	St Jude Medical	NHLBI, C.R. Bard, Berlex Laboratory, Boehringer-Ingelheim Pharmaceuticals, Guidant, Knoll Pharmaceuticals, Medtronic, Searle, Ventritex–St Jude Medical, Wyeth-Ayerst Laboratory	Guidant, University of Rochester School of Medicine and Dentistry

Abbreviations: DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator In Acute Myocardial Infarction Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; NHLBI, National Heart, Lung, and Blood Institute; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

Table 2. Baseline Characteristics of Patients in Trials Included in the Analysis

Characteristics	DEFINITE ²²	SCD-HeFT ²⁴	DINAMIT ²¹	MUSTT ¹⁷	MADIT II ¹⁹
No. randomized	458	1676	674	704	1232
Women, No. (%)	132 (28.8)	382 (22.8)	160 (23.7)	68 (9.7)	192 (15.9)
NICM, No. (%)	458 (100)	792 (47.3)	0	0	0
Mean duration of follow-up, mo	29	45.5	30	39	20
Demographics					
Mean age, y	58.3	60.1	61.5	66.5	64.5
NYHA class III/IV, %	21.0	30.0	13.2	24.5	28.5
Mean duration of CHF	2.8 y	24.5 mo	<30 d	>3 mo	>3 mo
Mean LVEF, %	21.4	24.7	28.0	29.5	23.0
Medications at baseline, %					
β-Blocker	84.9	69.0	86.8	40.0	70.0
ACE inhibitor or ARB	96.7	96.3	94.9	74.5	69.6
Design	ICD vs pharmacologic therapy	ICD vs amiodarone hydrochloride vs placebo	ICD vs pharmacologic therapy	Electrophysiologic test-guided ICD vs pharmacologic therapy	ICD vs pharmacologic therapy
Primary end point	Total mortality	Total mortality	Total mortality	Cardiac arrest or death from arrhythmia	Total mortality
Control 1-year mortality, %	6.2	7.2	6.9	7.5	7.2
Transvenous ICD, %	100	100	100	100	100

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, congestive heart failure; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator In Acute Myocardial Infarction Trial; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

COMMENT

The target therapy in the termination of lethal ventricular arrhythmias in patients with heart failure has become ICD therapy. We found that ICD therapy for the primary prevention of SCD in women does not show any benefit to all-cause mortality (HR, 1.01; 95% CI, 0.76-1.33; $P=0.95$). There is uncertainty in regard to ways to optimize therapy, when one considers the underlying epidemiologic differences that exist between men and women

in terms of risk stratification and prevention of SCD. This factor has only been partially addressed by the published medical literature.

Data from a sample of Medicare beneficiaries with heart failure and reduced LVEF who met the criteria for ICD implantation for the primary prevention of SCD revealed that only 8.6 per 1000 women received an ICD compared with 32.3 per 1000 men within 1 year of diagnosis.²⁸ Similarly, data from the Get With The Guidelines heart failure database examined the sex disparities

Table 3. Sex Differences in Mortality Rates Between ICD Implantation and Medical Therapy Groups

Trial	Men, %		Women, %	
	ICD	Medical Therapy	ICD	Medical Therapy
MADIT II ²⁰	16	20	16	30
MUSTT ¹⁸	41	50	53	34
SCD-HeFT ²⁵	22.8	31.0	18.9	21.4
DEFINITE ²³	11	18	18	16
DINAMIT ²¹	NR	NR	NR	NR

Abbreviations: DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator In Acute Myocardial Infarction Trial; ICD, implantable cardioverter-defibrillator; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; NR, not reported; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

of ICD therapy for the primary prevention of SCD. Women represented only 27.2% of patients of the total population who received ICDs and 37.8% of patients who did not.²⁹ The exact reasons for the significant sex differences in ICD implantation rates are not well established, but perhaps some of this disparity is driven by the paucity of data for women in randomized clinical trials of ICD therapy.³⁰

Most clinical trials have been heavily weighted toward men; therefore, generalization of the results to women remains questionable. The best answer to this problem would be to perform a clinical trial that specifically targets women with heart failure to test the hypothesis of whether ICD implantation reduces their overall mortality rate. However, given the current guideline recommendations of ICD therapy for both primary and secondary prevention of SCD, it may be difficult to propose such a trial.³¹ However, on the basis of our findings it seems that a trial targeting women is needed, and a meta-analysis such as ours may be an appropriate first step to explore this hypothesis.

After the analysis of clinical trials of ICD implantation vs medical therapy for the primary prevention of SCD in women with heart failure, our meta-analysis revealed no significant decrease in the overall mortality rate for women. Although heterogeneity existed among the trials, most of the population studied reflects the patient population that we encounter on a daily basis. There are several possible explanations for our observation.

It has been established that women have a lower risk of SCD compared with men. In the Framingham Study, among those who have coronary artery disease, women had only one-fourth the risk of SCD compared with men.³² Although the underlying mechanism for the difference in mortality rates is not clearly understood, there are some postulated explanations for this observed difference.

There appear to be clear sex differences in arrhythmia susceptibility. Postinfarction, female patients are less likely to experience ventricular tachyarrhythmias, and this observation is independent of measured baseline clinical, electrocardiographic, and electrophysiologic characteristics.³³ Sex differences in temporal parameters of repolarization and in arrhythmogenic substrate may ex-

plain the observed differences in arrhythmia susceptibility in women and predict the risk of SCD in patients postinfarction who have severe left ventricular dysfunction.³⁴

Data from animal models have demonstrated a smaller repolarizing, slowly delayed, rectifier potassium channel current in female rabbits, which may explain the differences in repolarization in female humans.³⁵ There are also sex differences in sarcoplasmic reticulum, calcium handling,³⁶ calcium-channel density,³⁷ the repolarization of potassium currents,³⁸ autonomic modulation,³⁹ and the sodium-calcium exchanger⁴⁰ that may contribute to the decreased propensity for triggered arrhythmias in women. Many of the mechanisms described for sex differences in electrophysiologic properties are influenced by hormonal differences between men and women.^{38,41-43}

Women with advanced heart failure and systolic dysfunction who are enrolled in clinical trials tend to be older and are more likely to have nonischemic heart failure.⁴⁴ Women present with more severe heart failure symptoms, higher systolic blood pressure, and a higher incidence of diabetes mellitus.⁴⁴ Although women have worse clinical status compared with men, they experience fewer episodes of spontaneous ventricular arrhythmias²⁰ despite being more susceptible to drug-induced proarrhythmia.⁴⁵ In fact, women appear to have more severe comorbidities with more competing causes of death compared with men, which makes this population less susceptible to SCD. The decreased overall rate of SCD combined with an increased rate of other competing causes of death leads to a smaller net benefit derived from ICDs in women with advanced heart failure and reduced LVEF. Therefore, a larger number of patients may be required to exhibit a statistically significant decrease in mortality. To detect a statistically significant decrease in mortality based on the differences observed in the SCD-HeFT, we would need to conduct a study with more than 4000 women randomized to ICD implantation or placebo therapy. Assuming a 2.5% absolute reduction in overall mortality rates, the number needed to treat is estimated to be 40 women for every life saved by an ICD compared with 12 for men. This information highlights the fact that even though the benefit of ICD therapy in women may be less than in men, it may represent a clinically significant reduction in mortality for the female population. Further economic and social analyses must be performed with women to determine the cost-effectiveness of this therapy in women.

Our analysis also does not take into account the potential differences in baseline characteristics of women. Previous studies^{25,46} have reported that women who receive ICDs may have substantial differences in their baseline characteristics from men who receive the same therapy. The more appropriate way to overcome this difference in baseline characteristics is to conduct a meta-analysis by the use of individual patient data.

Four studies were excluded because they did not report an outcome of interest for women. We did not contact the authors to obtain unpublished data because we believed that doing so might introduce bias in our report by the introduction of data that have not undergone an intensive peer-review process. Moreover, exclusion of unpublished data often leads to overestimation of the treatment effect of meta-analysis.⁴⁷ Also 3 of the 4



Figure 2. Mortality among men with systolic dysfunction randomized to implantable cardioverter-defibrillator (ICD) implantation vs medical therapy for the primary prevention of sudden cardiac death. Error bars indicate 95% confidence intervals (CIs). Diamonds designate overall effect and squares, the effect for each individual study; both represent the width of the confidence interval. DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator In Acute Myocardial Infarction Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

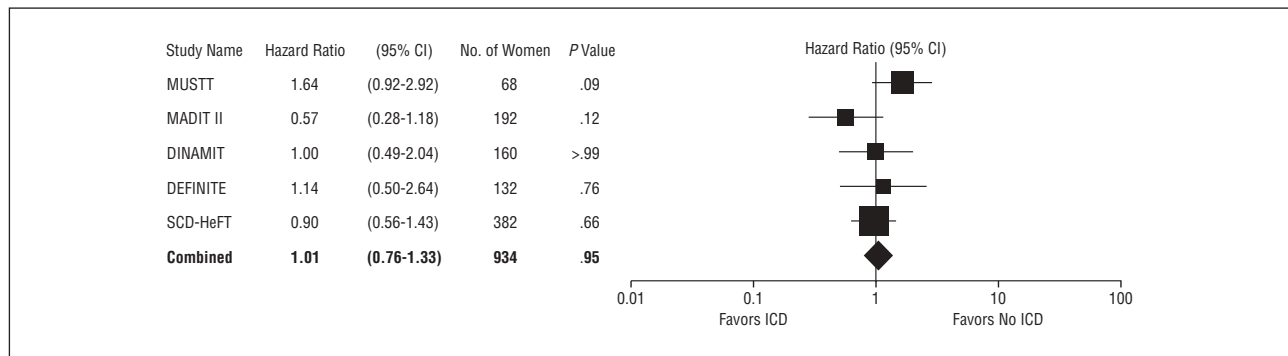


Figure 3. Mortality among women with systolic dysfunction randomized to implantable cardioverter-defibrillator (ICD) implantation vs medical therapy for the primary prevention of sudden cardiac death. Error bars indicate 95% confidence intervals (CIs). Diamonds designate overall effect and squares, the effect for each individual study; both represent the width of the confidence interval. DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator In Acute Myocardial Infarction Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

trials reported negative results, which would most likely decrease the observed effect if these patients were included in the meta-analysis.

Clinical trials of ICD therapy included in our analysis used the total mortality rate as their primary end point. However, ICDs can only affect mortality by the prevention of death owing to malignant arrhythmias. Therefore, the benefits observed in the reduction of overall mortality rates are owing solely to the prevention of arrhythmic death.³¹ However, arrhythmic death as an end point for women was not exclusively reported for all the clinical trials analyzed. This point warrants further investigation to determine whether there is a reduction in arrhythmic death among women with heart failure who receive an ICD for the primary prevention of SCD.

Our analysis demonstrated that ICD therapy for the primary prevention of SCD in women does not affect all-cause mortality rates. There may be several explanations for this important and surprising finding. Further studies are warranted to investigate the reasons for this observation and to elucidate the female population who may benefit most from ICD therapy.

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REFERENCES

- American Heart Association. Heart Disease and Stroke—2008 Update At-a-Glance statistics. 2008. http://www.americanheart.org/downloadable/heart/1200078608862HS_Stats%202008.final.pdf. Accessed December 20, 2008.
- Lloyd-Jones DM, Larson MG, Leip EP, et al; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106(24):3068-3072.

3. Mark DB, Nelson CL, Anstrom KJ, et al; SCD-HeFT Investigators. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation*. 2006;114(2):135-142.
4. Zwanziger J, Hall WJ, Dick AW, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol*. 2006;47(11):2310-2318.
5. Noyes K, Corona E, Zwanziger J, et al; Multicenter Automatic Defibrillator Implantation Trial II. Health-related quality of life consequences of implantable cardioverter/defibrillators: results from MADIT II. *Med Care*. 2007;45(5):377-385.
6. Haynes RB, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Inform Assoc*. 1994;1(6):447-458.
7. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. 2008. www.cochrane-handbook.org. Accessed August 2, 2008.
8. Moher D, Fortin P, Jadad AR, et al. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet*. 1996;347(8998):363-366.
9. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials*. 1995;16(1):62-73.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
12. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.
13. Bänsch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation*. 2002;105(12):1453-1458.
14. Strickberger SA, Hummel JD, Bartlett TG, et al; AMIOVIRT Investigators. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. *J Am Coll Cardiol*. 2003;41(10):1707-1712.
15. Bigger JT Jr; Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med*. 1997;337(22):1569-1575.
16. Moss AJ, Hall WJ, Cannom DS, et al; Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996;335(26):1933-1940.
17. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G; Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med*. 1999;341(25):1882-1890.
18. Russo AM, Stamato NJ, Lehmann MH, et al; MUSTT Investigators. Influence of gender on arrhythmia characteristics and outcome in the Multicenter Unsustained Tachycardia Trial. *J Cardiovasc Electrophysiol*. 2004;15(9):993-998.
19. Moss AJ, Zareba W, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346(12):877-883.
20. Zareba W, Moss AJ, Jackson Hall W, et al; MADIT II Investigators. Clinical course and implantable cardioverter/defibrillator therapy in postinfarction women with severe left ventricular dysfunction. *J Cardiovasc Electrophysiol*. 2005;16(12):1265-1270.
21. Hohnloser SH, Kuck KH, Dorian P, et al; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med*. 2004;351(24):2481-2488.
22. Kadish A, Dyer A, Daubert JP, et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med*. 2004;350(21):2151-2158.
23. Albert CM, Quigg R, Saba S, et al; DEFINITE Investigators. Sex differences in outcome after implantable cardioverter/defibrillator implantation in nonischemic cardiomyopathy. *Am Heart J*. 2008;156(2):367-372.
24. Bardy GH, Lee KL, Mark DB, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225-237.
25. Russo AM, Poole JE, Mark DB, et al. Primary prevention with defibrillator therapy in women: results from the Sudden Cardiac Death in Heart Failure Trial. *J Cardiovasc Electrophysiol*. 2008;19(7):720-724.
26. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA*. 2004;292(23):2874-2879.
27. Yusuf S, Garg R, Zucker D. Analyses by the intention-to-treat principle in randomized trials and databases. *Pacing Clin Electrophysiol*. 1991;14(12):2078-2082.
28. Hernandez AF, Fonarow GC, Liang L, et al. Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure. *JAMA*. 2007;298(13):1525-1532.
29. Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF, Schulman KA. Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death. *JAMA*. 2007;298(13):1517-1524.
30. Redberg RF. Disparities in use of implantable cardioverter-defibrillators: moving beyond process measures to outcomes data. *JAMA*. 2007;298(13):1564-1566.
31. Curtis AB. Prevention of sudden cardiac death: when is a woman just like a man? *J Cardiovasc Electrophysiol*. 2004;15(9):999-1001.
32. Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. *Am Heart J*. 1998;136(2):205-212.
33. Lampert R, McPherson CA, Clancy JF, Caulin-Glaser TL, Rosenfeld LE, Batsford WP. Gender differences in ventricular arrhythmia recurrence in patients with coronary artery disease and implantable cardioverter-defibrillators. *J Am Coll Cardiol*. 2004;43(12):2293-2299.
34. Haigney MC, Zareba W, Nasir JM, et al; MADIT II Investigators. Gender differences and risk of ventricular tachycardia or ventricular fibrillation. *Heart Rhythm*. 2009;6(2):180-186.
35. Liu X-K, Katchman A, Drici M-D, et al. Gender difference in the cycle length-dependent QT and potassium currents in rabbits. *J Pharmacol Exp Ther*. 1998;285(2):672-679.
36. Dash R, Frank KF, Carr AN, Moravec CS, Kranias EG. Gender influences on sarcoplasmic reticulum Ca²⁺-handling in failing human myocardium. *J Mol Cell Cardiol*. 2001;33(7):1345-1353.
37. Vizgirda VM, Wahler GM, Sondgeroth KL, Ziolo MT, Schwartz DW. Mechanisms of sex differences in rat cardiac myocyte response to β -adrenergic stimulation. *Am J Physiol Heart Circ Physiol*. 2002;282(1):H256-H263.
38. Song M, Helguera G, Eghbali M, et al. Remodeling of Kv4.3 potassium channel gene expression under the control of sex hormones. *J Biol Chem*. 2001;276(34):31883-31890.
39. Nakagawa M, Ooie T, Ou B, et al. Gender differences in autonomic modulation of ventricular repolarization in humans. *J Cardiovasc Electrophysiol*. 2005;16(3):278-284.
40. Wei SK, McCurley JM, Hanlon SU, Haigney MC. Gender differences in Na/Ca exchanger current and β -adrenergic responsiveness in heart failure in pig myocytes. *Ann N Y Acad Sci*. 2007;1099:183-189.
41. Hara M, Danilo P Jr, Rosen MR. Effects of gonadal steroids on ventricular repolarization and on the response to E4031. *J Pharmacol Exp Ther*. 1998;285(3):1068-1072.
42. Chen YJ, Lee SH, Hsieh MH, et al. Effects of 17 β -estradiol on tachycardia-induced changes of atrial refractoriness and cisapride-induced ventricular arrhythmia. *J Cardiovasc Electrophysiol*. 1999;10(4):587-598.
43. Stumpf WE, Sar M, Aumüller G. The heart: a target organ for estradiol. *Science*. 1977;196(4287):319-321.
44. Frazier CG, Alexander KP, Newby LK, et al. Associations of gender and etiology with outcomes in heart failure with systolic dysfunction: a pooled analysis of 5 randomized control trials. *J Am Coll Cardiol*. 2007;49(13):1450-1458.
45. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA*. 1993;270(21):2590-2597.
46. Kudenchuk PJ, Bardy GH, Poole JE, et al. Malignant sustained ventricular tachyarrhythmias in women: characteristics and outcome of treatment with an implantable cardioverter/defibrillator. *J Cardiovasc Electrophysiol*. 1997;8(1):2-10.
47. Cook DJ, Guyatt GH, Ryan G, et al. Should unpublished data be included in meta-analyses? current convictions and controversies. *JAMA*. 1993;269(21):2749-2753.