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 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 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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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. 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 Clinical Trials.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 defibrillator, implantable, heart failure, and randomized controlled trial. We also used a previously developed MEDLINE search strategy 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. 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.

### 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 scale 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. The Q test and I² index were used to check for quantitative heterogeneity, 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. 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, the Amiodarone vs Implantable Cardioverter-Defibrillator Trial, the Coronary Artery Bypass Graft Patch Trial, and the Multicenter Automatic Defibrillator Implantation Trial (MADIT). 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), MADIT II, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), the Defibrillators in Non-Ischemic Cardiomyopathy Treat-
Amiodarone hydrochloride, or placebo; a total of 1676 randomized patients with heart failure to therapy with ICD, medical therapy in a 2-arm study design. The SCD-HeFT randomized patients with nonischemic cardiomyopathy with an LVEF of 36% or less and ambient arrhythmia to ICD implantation or medical therapy and bias the results toward a lesser benefit of ICD therapy in an intent-to-treat analysis. 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. 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. There was no evidence of significant publication bias (P = .81 by the Beg and Mazumdar rank-correlation test).
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

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

<table>
<thead>
<tr>
<th>Internal Validity</th>
<th>DEFINITE22</th>
<th>SCD-HeFT24</th>
<th>DINAMIT21</th>
<th>MUSTT17</th>
<th>MADIT II19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, %</td>
<td>100</td>
<td>100</td>
<td>100 (Partial follow-up for 4 patients in the control group)</td>
<td>99.4</td>
<td>99.8</td>
</tr>
<tr>
<td>Crossover to ICD therapy, No. (%)</td>
<td>23/229 (10.0)</td>
<td>188/1692 (11.1)</td>
<td>0/042</td>
<td>46/353 (13.0)</td>
<td>22/490 (4.5)</td>
</tr>
<tr>
<td>Crossover to pharmacologic therapy, No. (%)</td>
<td>4/229 (1.7)</td>
<td>163/829 (19.5)</td>
<td>20/332 (6.0)</td>
<td>46/351 (13.1)</td>
<td>32/742 (4.3)</td>
</tr>
<tr>
<td>Intent to treat</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Events committee</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jadad scale score</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Sponsorship</td>
<td>St Jude Medical, Medtronic, Wyeth-Ayerst Laboratory, Knoll Pharmaceuticals</td>
<td>St Jude Medical, Medtronic, Wyeth-Ayerst Laboratory</td>
<td>St Jude Medical, Medtronic, Wyeth-Ayerst Laboratory</td>
<td>NHLBI, C.R. Bard, Berlex Laboratory, Boehringer-Ingelheim Pharmaceuticals, Guidant, Knoll Pharmaceuticals, Medtronic, Merck, Searle, Ventritex-St Jude Medical, Wyeth-Ayerst Laboratory</td>
<td>Guidant, University of Rochester School of Medicine and Dentistry</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DEFINITE22</th>
<th>SCD-HeFT24</th>
<th>DINAMIT21</th>
<th>MUSTT17</th>
<th>MADIT II19</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomized</td>
<td>458</td>
<td>1676</td>
<td>674</td>
<td>704</td>
<td>1232</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>132 (28.8)</td>
<td>382 (22.8)</td>
<td>160 (23.7)</td>
<td>68 (9.7)</td>
<td>192 (15.9)</td>
</tr>
<tr>
<td>NICM, No. (%)</td>
<td>458 (100)</td>
<td>792 (47.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean duration of follow-up, mo</td>
<td>29</td>
<td>45.5</td>
<td>30</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>58.3</td>
<td>60.1</td>
<td>61.5</td>
<td>66.5</td>
<td>64.5</td>
</tr>
<tr>
<td>NYHA class III/IV, %</td>
<td>21.0</td>
<td>30.0</td>
<td>13.2</td>
<td>24.5</td>
<td>28.5</td>
</tr>
<tr>
<td>Mean duration of CHF</td>
<td>2.8 y</td>
<td>24.5 mo</td>
<td>&lt;30 d</td>
<td>&gt;3 mo</td>
<td>&gt;3 mo</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>21.4</td>
<td>24.7</td>
<td>28.0</td>
<td>29.5</td>
<td>23.0</td>
</tr>
<tr>
<td>Medications at baseline, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>84.9</td>
<td>69.0</td>
<td>86.8</td>
<td>40.0</td>
<td>70.0</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>96.7</td>
<td>96.3</td>
<td>94.9</td>
<td>74.5</td>
<td>69.6</td>
</tr>
<tr>
<td>Design</td>
<td>ICD vs pharmacologic therapy</td>
<td>ICD vs amiodarone hydrochloride vs placebo</td>
<td>ICD vs pharmacologic therapy</td>
<td>Electrophysiologic test-guided ICD vs pharmacologic therapy</td>
<td>ICD vs pharmacologic therapy</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Total mortality</td>
<td>Total mortality</td>
<td>Total mortality</td>
<td>Cardiac arrest or death from arrhythmia</td>
<td>Total mortality</td>
</tr>
<tr>
<td>Control 1-year mortality, %</td>
<td>6.2</td>
<td>7.2</td>
<td>6.9</td>
<td>7.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Transvenous ICD, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

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.
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. Women present with more severe heart failure symptoms, higher systolic blood pressure, and a higher incidence of diabetes mellitus. Although women have worse clinical status compared with men, they experience fewer episodes of spontaneous ventricular arrhythmias despite being more susceptible to drug-induced proarrhythmia. 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 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. Also 3 of the 4...
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. 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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Additional Contributions: Fred Morady, MD, critically reviewed the manuscript.

REFERENCES


22. Mad H...