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

Hamid Ghanbari, MD; Ghassan Dalloul, MD; Reema Hasan, MD; Marcos Daccarett, MD, MSc; Souheil Saba, MD; Shukri David, MD; Christian Machado, MD

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.

Arch Intern Med. 2009;169(16):1500-1506
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 strategy\(^6\) 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.\(^8\)

#### 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\(^9\) 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

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-
amiodarone hydrochloride, or placebo; a total of 1676
domized patients with heart failure to therapy with ICD,
cal therapy in a 2-arm study design.22 The SCD-HeFT ran-
less and ambient arrhythmia to ICD implantation or medi-
nonischemic cardiomyopathy with an LVEF of 36% or
these trials. The DEFINITE trial randomized patients with
meta-analysis. CRT indicates chronic resynchronization therapy.

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 med-
tical therapy in a 2-arm study design.22 The SCD-HeFT ran-
donized 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 nonsus-
tained ventricular tachycardia. Patients in whom sust-
vained ventricular tachyarrhythmias were induced by
programmed stimulation were randomly assigned to re-
cive either antiarrhythmic therapy, with the inclusion
of drugs and ICDs, as indicated by the results of elec-
trophysiologic 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 pa-
tients who had an acute myocardial infarction with an
LVEF of 35% or less and impaired cardiac autonomic func-
tion 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 set-
ing. Table 1 summarizes the baseline characteristics
of the patients enrolled in these trials. Despite the sig-
nificant heterogeneity noted in these trials, we believed
that there were sufficient similarities to warrant their in-
cclusion in the quantitative portion of our meta-analysis.

All 5 of the trials included in the analysis were of com-
parable quality. None of the trials reported a significant
interaction between sex and ICD therapy on overall mor-
tality. The intervention (ICD implantation) was a surgi-
cal procedure; therefore, allocation concealment and
masking were not possible in these trials.26 All trials used
either an independent or masked committee for adjudica-
tion of events. All trials used intent-to-treat analyses
and in most cases provided detailed accounting of drop-
outs and crossovers. Even though these trials had wide
variations in crossover rates, we expected that cros-
overs 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 methodo-
logic quality for each trial. Table 3 summarizes the mor-
tality rates reported for the included trials and com-
paring the sex differences in the ICD implantation vs
placebo groups. The companies whose device was the sub-
ject of study provided at least some part of the funding
for each trial.

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

QUANTITATIVE FINDINGS

A total of 3810 men were included in our analysis. A sta-
tistically significant decrease in mortality rates was found
in men with heart failure and reduced LVEF who re-
ceived ICDs for the primary prevention of SCD com-
pared 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, I² = 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 demon-
strate 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, I² = 26.62).
We performed several sensitivity analyses to assess the
effect of heterogeneity in trial design and patient selec-
tion 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 stan-
dard error for each trial and mathematically by the use
of an adjusted rank-correlation test.12 There was no evi-
dence of significant publication bias (P = .81 by the Beg-
and Mazumdar rank-correlation test).
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...
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. 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.

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. 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. 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. Sex differences in temporal parameters of repolarization and in arrhythmogenic substrate may explain the observed differences in arrhythmia susceptibility in women and predict the risk of SCD in patients postinfarction who have severe left ventricular dysfunction.

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. There are also sex differences in sarcoplasmic reticulum, calcium handling, calcium-channel density, the repolarization of potassium currents, autonomic modulation, and the sodium-calcium exchanger 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.

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.
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. Therefore, 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.

Accepted for Publication: May 22, 2009.

Correspondence: Christian Machado, MD, Department of Cardiology, Providence Hospital Heart Institute and Medical Center, 16001 W Nine Mile Rd, Southfield, MI 48075 (Christian.Machado@providence-stjohnhealth.org).

Author Contributions: Study concept and design: Ghanbari, Dalloul, Hasan, Saba, and Machado. Acquisition of data: Ghanbari, Dalloul, and Hasan. Analysis and interpretation of data: Ghanbari, Dalloul, Hasan, Daccarett, David, and Machado. Drafting of the manuscript: Ghanbari, Dalloul, Hasan, Saba, and Machado. Critical revision of the manuscript for important intellectual content: Ghanbari, Dalloul, Hasan, Daccarett, David, and Machado. Statistical analysis: Dalloul and David. Administrative, technical, and material support: Ghanbari, Dalloul, Hasan, Daccarett, David, and Machado. Study supervision: Daccarett, Saba, David, and Machado.

Financial Disclosure: None reported.

Additional Contributions: Fred Morady, MD, critically reviewed the manuscript.

REFERENCES


