Effectiveness of Implantable Cardiorter-Defibrillators in Patients With Ischemic Heart Disease and Left Ventricular Dysfunction

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Background: Implantable cardioverter-defibrillators (ICDs) have been shown to reduce mortality in patients with ischemic heart disease and left ventricular dysfunction. To investigate the generalizability of this mortality reduction, we examined the effectiveness of ICDs in clinical practice.

Methods: We developed a prospective multicenter cohort of 770 patients with ischemic left ventricular dysfunction (ejection fraction ≤35%) and without a history of ventricular arrhythmia, of whom 395 (52%) received ICDs. Mean ± SD follow-up was 27 ± 12 months. We assessed the degree to which ICDs decreased mortality risk using Cox proportional hazards analyses that controlled for clinical predictors of death, receipt of ICD (a propensity score analysis), and predictors of arrhythmic death (including electrophysiology variables).

Results: Multivariate Cox analyses showed that those with ICDs had significantly lower all-cause mortality (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.33-0.86). This mortality reduction was mediated through dramatically lower arrhythmia-related mortality (HR, 0.35; 95% CI, 0.17-0.73), with no significant effect on cardiovascular nonarrhythmic (HR, 0.81; 95% CI, 0.34-1.96) and noncardiovascular (HR, 0.76; 95% CI, 0.29-2.05) mortality. No differences were found between the ICD and non-ICD groups for a composite outcome of all-cause mortality, appropriate ICD shocks, or documented symptomatic ventricular arrhythmia, which suggests that the 2 groups had similar baseline risk for life-threatening arrhythmic events (HR, 0.96; 95% CI, 0.63-1.45).

Conclusion: In clinical practice, ICDs appear to reduce all-cause and arrhythmic rates of mortality at levels similar to those found in primary prevention trials.

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compared with medical therapy alone.10,11 Because of this potential cost to society, CMS has proposed developing a registry to further examine the benefits of ICD therapy in the nontrial setting.12 However, such a registry would only include those patients who receive ICDs and would therefore not be able to rigorously examine ICD effectiveness because there would be no control group for comparison.

Given the cost and policy implications of the CMS decision and the need for effectiveness studies to ensure no dilution of benefit from ICD efficacy trials, we undertook an effectiveness study in a nontrial patient population with ischemic heart disease and left ventricular dysfunction to examine the generalizability of the mortality benefit found with prophylactic ICD placement in efficacy trials.

METHODS

PATIENT POPULATION

A multicenter prospective cohort of consecutive patients with ischemic heart disease and left ventricular dysfunction was developed from 7 cardiology outpatient clinics and coordinated by The Ohio Heart and Vascular Center and the Lindner Clinical Trials Center. The main objective of the cohort was to examine the prognostic utility of microvolt T-wave alternans (MTWA) screening, with a secondary objective of assessing the effectiveness of ICD therapy in the community practice setting. As a result, patients had to be in sinus rhythm (for MTWA assessment) for cohort enrollment.

Enrollment occurred from March 2001 to June 2004 with follow-up through September 2005. For our study cohort, we included those patients 18 years or older who met the criteria for ischemic heart disease (defined as coronary artery disease on cardiac catheterization with >70% stenosis in >1 coronary artery, history of myocardial infarction, or history of angio-plasty or coronary bypass graft surgery) and left ventricular dysfunction (defined as left ventricular ejection fraction [LVEF] ≤35% determined via surface echocardiogram [≥90%], ventriculogram, or nuclear imaging). Patients with prior coronary revascularization within the past 3 months, a myocardial infarction within the past month, a history of sustained ventricular arrhythmia (≥30 beats), or terminal illnesses such as cancer were excluded.

BASELINE DATA COLLECTION

Baseline patient characteristics were collected at initial enrollment and included age, sex, LVEF, QRS duration, and clinical variables (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic renal insufficiency, peripheral vascular disease, and history of myocardial infarction, stroke, transient ischemic attack, atrial fibrillation, symptomatic heart failure, and unexplained syncope). In addition, baseline medication usage (aspirin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, spironolactone, statin, digoxin, diuretic, and classes 1 and 3 antiarrhythmic agents), revascularization history (angioplasty or coronary bypass graft surgery), and clinic site data were collected.

During the baseline visit, patients underwent noninvasive screening with both MTWA and Holter studies. All MTWA tests were interpreted according to standard criteria by an expert reader blinded to patient characteristics and clinical outcomes, and results were classified as either negative (33%) or nonnegative (positive [46%] and indeterminate [21%; not re-tested]).13 Holter monitoring (24-48 hours) was used for detection of nonsustained ventricular tachycardia (VT), which was defined as more than 100 beats per minute for 3 or more consecutive beats and less than 30 seconds.

Further testing with EPS in the cohort was based on clinical criteria and noninvasive study results. For those patients undergoing invasive EPS, a positive finding was defined as (1) inducible, sustained, monomorphic VT of cycle length 230 milliseconds or longer or (2) inducible ventricular fibrillation, polymorphic VT, or ventricular flutter (monomorphic VT with a cycle length <230 milliseconds) with 2 or fewer ventricular extrastimuli. Because not all patients underwent an EPS, 2 dummy variables were created to reflect 3 levels of EPS status in the cohort: no test, a positive finding, and a negative finding. Finally, ICD implantation in our cohort was performed at the discretion of the attending physician and was primarily (93%) of all ICDs implanted based on a positive EPS result, an abnormal Holter result, or a QRS greater than 120 milliseconds in the post-MADIT-II trial period (after mid-2002).

All patients in the study gave informed consent, and the study was approved by the institutional review board at the Christ Hospital and its affiliated clinics (Cincinnati, Ohio).

CLINICAL END POINTS AND FOLLOW-UP

The primary end point was all-cause mortality, which was determined through quarterly clinic visits in 97.3% of cases, routine review of office charts in 100%, telephone contact with patient in 99.4%, and annual query of the US National Death Index (using first and last name, Social Security number, sex, state location, and date of birth) in 100%. Secondary end points included cause-specific mortality, appropriate ICD shock therapy in patients with ICD, and documented symptomatic ventricular arrhythmia not terminated by ICD therapy. Cause-specific mortality was classified as arrhythmic or nonarrhythmic via a modified Hinkle-Thaler system.16 Arrhythmic deaths included unwitnessed deaths (if the patient’s condition was stable when last observed within 24 hours before death), witnessed instantaneous deaths, and sequelae of cardiac arrest. Nonarrhythmic deaths were further subclassified by cause as cardiovascular nonarrhythmic or noncardiovascular. Cause-specific mortality was adjudicated by an independent panel of 2 investigators blinded to a patient’s clinical characteristics, ICD status, and EPS results. If consensus could not be reached, the decision was referred to a third and senior committee member. Finally, ICDs were evaluated at routine visits, and appropriate ICD shocks were defined as shocks for documented VT or ventricular fibrillation.

The index date for the non-ICD cohort was the date of cohort enrollment. To avoid survival bias against the non-ICD group (since all patients with ICD had to survive until the time of ICD implantation), the index date for the ICD group was the date of ICD implantation, with the median time from cohort enrollment to ICD implantation being 58 days. As survival may not be linear over time, we repeated the analyses such that deaths in the non-ICD group were excluded during the first 58 days (n = 3) and the index date was the enrollment date in the ICD group and found that the results were similar (results not shown).

STATISTICAL ANALYSIS

Unadjusted Analysis

Baseline characteristics in the ICD and non-ICD groups were compared using t tests for continuous variables and χ² tests for
The study cohort was made up of 770 patients, of whom 395 (52%) received ICDs. Mean ± SD follow-up times were 28 ± 13 months for the non-ICD group and 26 ± 12 months for the ICD group (excluding a median time of 2 months from enrollment to ICD placement). Mortality follow-up was achieved for all cohort patients, and appropriate shock follow-up was achieved for 98% of all ICD patients.

A comparison of baseline characteristics is given in Table 1. An EPS was performed in 48% of the study cohort (376/770). Patients with ICDs had lower LVEFs; were symptomatic heart failure, and a history of myocardial infarction; and a history of congestive heart failure. Patients with ICDs also had a higher prevalence of microvolt T-wave alternans, prolonged QRS for more than 120 milliseconds, and abnormal Holter 

Table 1. Baseline Characteristics for Study Cohort*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICD (n = 395)</th>
<th>Non-ICD (n = 375)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>66.8 ± 9.9</td>
<td>67.5 ± 11.1</td>
<td>.37</td>
</tr>
<tr>
<td>Men</td>
<td>85.9</td>
<td>78.9</td>
<td>.01</td>
</tr>
<tr>
<td>LVEF, mean ± SD, %</td>
<td>26.2 ± 6.0</td>
<td>28.3 ± 6.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Clinic site, No. (%)</td>
<td></td>
<td></td>
<td>.78</td>
</tr>
<tr>
<td>1</td>
<td>49 (12.4)</td>
<td>48 (12.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>161 (40.7)</td>
<td>138 (36.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>89 (22.5)</td>
<td>90 (24.0)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>41 (10.4)</td>
<td>51 (13.6)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36 (9.1)</td>
<td>33 (8.8)</td>
<td></td>
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<tr>
<td>6</td>
<td>12 (3.0)</td>
<td>8 (2.1)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7 (1.8)</td>
<td>7 (1.9)</td>
<td></td>
</tr>
<tr>
<td>EP study performed, No. (%)</td>
<td>276 (69.9)</td>
<td>100 (26.7)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EP inducibility, No. (%)</td>
<td>216 (54.7)</td>
<td>16 (4.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>QRS &gt;120 ms</td>
<td>38.7</td>
<td>25.7</td>
<td>.001</td>
</tr>
<tr>
<td>Microvolt T-wave alternans</td>
<td>80.8</td>
<td>52.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Abnormal Holter findings</td>
<td>24.6</td>
<td>13.6</td>
<td>.001</td>
</tr>
<tr>
<td>CABG</td>
<td>57.1</td>
<td>55.2</td>
<td>.60</td>
</tr>
<tr>
<td>PTCA</td>
<td>52.5</td>
<td>49.6</td>
<td>.42</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>88.4</td>
<td>82.1</td>
<td>.01</td>
</tr>
<tr>
<td>Symptomatic CHF</td>
<td>76.5</td>
<td>66.9</td>
<td>.003</td>
</tr>
<tr>
<td>Atrial fibrillation history</td>
<td>14.9</td>
<td>14.9</td>
<td>.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36.9</td>
<td>38.1</td>
<td>.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.6</td>
<td>34.9</td>
<td>.63</td>
</tr>
<tr>
<td>COPD</td>
<td>8.6</td>
<td>5.9</td>
<td>.14</td>
</tr>
<tr>
<td>PVD</td>
<td>5.3</td>
<td>4.8</td>
<td>.75</td>
</tr>
<tr>
<td>Stroke and/or TIA</td>
<td>14.7</td>
<td>15.5</td>
<td>.75</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.5</td>
<td>2.9</td>
<td>.73</td>
</tr>
<tr>
<td>Syncope</td>
<td>14.9</td>
<td>16.8</td>
<td>.47</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>76.8</td>
<td>76.0</td>
<td>.80</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>85.6</td>
<td>83.5</td>
<td>.41</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>84.9</td>
<td>79.5</td>
<td>.05</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>19.2</td>
<td>13.9</td>
<td>.05</td>
</tr>
<tr>
<td>Statin</td>
<td>65.9</td>
<td>58.7</td>
<td>.04</td>
</tr>
<tr>
<td>Digoxin</td>
<td>41.7</td>
<td>26.9</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>67.2</td>
<td>62.9</td>
<td>.22</td>
</tr>
<tr>
<td>Class I AA</td>
<td>0.8</td>
<td>0.5</td>
<td>.70</td>
</tr>
<tr>
<td>Class III AA</td>
<td>8.3</td>
<td>8.5</td>
<td>.92</td>
</tr>
</tbody>
</table>

Abbreviations: AA, antiarrhythmic agent; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EP, electrophysiologic; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; ms, milliseconds; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; TIA, transient ischemic attack.

*Unless otherwise indicated, data are reported as percentage of patients.

categorical variables. Unadjusted all-cause mortality between the ICD and non-ICD groups was assessed with Kaplan-Meier analysis and tested with the log-rank test as well as with Cox proportional hazards analysis. Similar analyses were also performed for cause-specific mortality and for a composite end point of all-cause mortality, appropriate ICD shock therapy, or symptomatic ventricular arrhythmia.

Adjusted Analysis

Because nonrandomized cohort studies might have significant differences in baseline risk between the compared groups, and because multivariate analyses might not adequately adjust for such differences (ie, the ICD and non-ICD groups might not truly overlap in their mortality risk profiles),5,17 we used a propensity score analysis in our Cox proportional hazards models. A propensity score analysis is a statistical technique that examines factors that influence the likelihood of receiving a particular treatment (in this case, ICD implantation), thereby allowing for comparisons of patients with comparable risk.15,16

To generate the propensity score, multivariable logistic regression was used to model ICD placement (dependent variable) with the 3 independent variables most likely to influence the clinical decision to implant ICDs in our cohort (EPS testing, QRS duration >120 milliseconds, and abnormal Holter findings). The model provides the predicted probability (from 0 to 1) of receiving an ICD for each patient. A C-statistic, representing the area under the receiver operating characteristic curve, indicates how well the propensity score model predicted defibrillator receipt. Next, all study covariates (including clinic site) except the ones used in developing the propensity score were examined for univariate associations with death (P<.10) through Cox proportional hazards analysis. Significant variables in univariate analyses were then systematically evaluated with Cox proportional hazards regression analyses to generate a multivariate model (P<.05) and reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Age, LVEF, and propensity score were kept in the final model, regardless of level of significance.

The same Cox analyses were performed for arrhythmic, nonarrhythmic cardiovascular, and noncardiovascular mortality. Finally, as a sensitivity test to further assess the potential mechanism of benefit with ICD therapy, we equated an appropriate defibrillator shock in ICD patients and symptomatic ventricular arrhythmia in all cohort patients with death, and assessed whether ICD and non-ICD patients were exposed to similar baseline arrhythmic event risks by comparing their risk for a composite outcome of all-cause mortality, ICD shock, or symptomatic ventricular arrhythmia using Cox regression analyses similar to those previously described.

Because other factors beyond EPS testing, QRS duration, and abnormal Holter results may influence decisions for ICD implantation, we also created a full nonparsimonious propensity score model using all study covariates as independent variables to predict ICD placement (C-statistic = 0.876).5,19 Cox proportional hazards analyses for each of the aforementioned outcomes with this full propensity score were not found to be substantially different (results not shown).

All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).
In the ICD group, 93% of all subjects had at least 1 of the 3 characteristics used in the propensity score derivation (positive EPS finding, abnormal Holter finding, or QRS >120 milliseconds).

There were a total of 129 deaths (74 in the non-ICD group and 55 in the ICD group), of which 56 were arrhythmic (38 in the non-ICD group and 18 in the ICD group) and 32 were cardiovascular nonarrhythmic (17 in the non-ICD group and 15 in the ICD group) (Table 2). In addition, there were 35 patients with appropriate ICD shocks not associated with death in the ICD group, as well as 4 documented symptomatic ventricular arrhythmias not terminated by ICD therapy.

Univariate Cox models found that there was a nonsignificant trend toward higher survival in the ICD group for the primary end point of all-cause mortality (HR, 0.76; 95% CI, 0.53-1.08), and survival curves constructed with Kaplan-Meier analysis are depicted in the Figure. For cause-specific mortality, ICD therapy was associated with significantly lower arrhythmic mortality (HR, 0.49; 95% CI, 0.28-0.86) but had no significant impact on cardiovascular nonarrhythmic (HR, 0.85; 95% CI, 0.42-1.73) or noncardiovascular (HR, 1.26; 95% CI, 0.65-2.23) mortality.

Our propensity score, derived from the 3 variables most likely to predict ICD placement (EPS, QRS duration, and Holter monitor), showed good discrimination, with a C-statistic of 0.812. The variable most strongly associated with ICD placement was a positive EPS finding (Wald statistic of 0.812. The variable most strongly associated with ICD placement was a positive EPS finding (Wald statistic of 0.812)

Multivariate Cox proportional hazards analyses adjusted for propensity score showed that ICDs were associated with substantially reduced all-cause mortality (HR, 0.53; 95% CI, 0.33-0.86) (P = .01) (Table 3). These results did not change substantively when the study cohort was limited to patients with LVEF less than 30% (n = 538; HR, 0.54; 95% CI, 0.33-0.89) (P = .02). When confining the outcome to arrhythmic deaths only, we found that ICDs were associated with dramatic reductions in arrhythmic mortality (HR, 0.35; 95% CI, 0.17-0.73) (P = .005) (Table 4). However, no significant differences were found with ICD therapy for cardiovascular nonarrhythmic (HR, 0.81; 95% CI, 0.34-1.96) and noncardiovascular mortality (HR, 0.76; 95% CI, 0.29-2.05). Finally, when a composite outcome of all-cause mortality, appropriate ICD shocks, or symptomatic ventricular arrhythmia was examined, no significant differences were found between the ICD and non-ICD groups, which suggests that the 2 groups were exposed to similar baseline combined rates of mortality and arrhythmic events (HR, 0.96; 95% CI, 0.63-1.43).

We found that patients with ischemic heart disease and left ventricular dysfunction had substantially improved survival when they received a prophylactic ICD in clini-

Table 2. Summary of Study End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>ICD (n = 395)</th>
<th>Non-ICD (n = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, mean ± SD, mo</td>
<td>26 ± 12</td>
<td>28 ± 13</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>55 (13.9)</td>
<td>74 (19.7)</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>18 (4.5)</td>
<td>38 (10.1)</td>
</tr>
<tr>
<td>Nonarrhythmic CV</td>
<td>15 (3.8)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Non-CV</td>
<td>22 (5.6)</td>
<td>19 (5.1)</td>
</tr>
<tr>
<td>Symptomatic VT/VF</td>
<td>1 (0.3)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>ICD shocks</td>
<td>35 (8.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation.

*Unless otherwise indicated, data are reported as number (percentage) of patients.

Table 3. Multivariate Cox Proportional Hazards Model for All-Cause Mortality Adjusted for Propensity Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>0.53 (0.33-0.86)</td>
<td>.01</td>
</tr>
<tr>
<td>PS</td>
<td>1.47 (0.66-3.25)</td>
<td>.35</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.01-1.05)</td>
<td>.003</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95 (0.93-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PTCA</td>
<td>0.57 (0.39-0.82)</td>
<td>.003</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.51 (0.36-0.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>0.65 (0.41-1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>DM</td>
<td>1.42 (0.99-2.03)</td>
<td>.05</td>
</tr>
<tr>
<td>PVD</td>
<td>1.89 (0.96-3.72)</td>
<td>.07</td>
</tr>
<tr>
<td>CHF</td>
<td>2.09 (1.26-3.46)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PS, propensity score; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease.

*Implantable cardioverter-defibrillator therapy, higher LVEF, a history of PTCA or ACE or ARB usage, and aspirin usage were protective for all-cause mortality, whereas a higher PS, older age, DM, PVD, and symptomatic CHF were predictive for all-cause mortality. Age, LVEF, and PS were modeled as continuous variables.

Figure. Kaplan-Meier curves for the ICD (implantable cardioverter-defibrillator) and non-ICD groups for unadjusted all-cause mortality. Log-rank test statistic = 2.4, P = .12.

Comment
retrospective design, lack of adjustment for several key vari-
ations can be successfully translated into routine prac-
tice without a substantial dilution of benefits. Recently, CMS expanded ICD coverage to primary pre-
vention patients meeting defined criteria of ischemic heart
disease and left ventricular dysfunction, regardless of QRS
duration. All patients in this cohort were enrolled prior
to this coverage expansion decision and publication of the
SCD-HeFT trial results, while a significant number were
enrolled prior to publication of MADIT-II. At that time, rou-
tine prophylactic ICD placement for primary prevention
without demonstrated inducibility on EPS was neither stan-
dard of care nor reimbursed by CMS. Since the recent CMS
decision, however, it may be very difficult to conduct a rig-
orous prospective effectiveness study similar to that pre-
sented here because of broader ICD use and greater selec-
tion biases as to who receives an ICD. In a prior effectiveness
study of ICDs among high-risk secondary prevention pa-
tients with ischemic heart disease and heart failure, we also
found that the mortality reduction benefit seen with ICDs
remained robust outside of trial settings. However, that
study evaluated only patients with a history of ventricular
arrhythmia (secondary prevention) and was limited by its
retrospective design, lack of adjustment for several key vari-
ables (LVEF and complete medication data), and its ex-
amination of primarily all-cause mortality. In addition, a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.76 (0.53-1.08)</td>
<td>0.53 (0.33-0.86)</td>
<td>.009</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>0.49 (0.28-0.86)</td>
<td>0.35 (0.17-0.73)</td>
<td>.005</td>
</tr>
<tr>
<td>CV nonarrhythmic</td>
<td>0.85 (0.42-1.73)</td>
<td>0.81 (0.34-1.96)</td>
<td>.64</td>
</tr>
<tr>
<td>Non-CV</td>
<td>1.26 (0.65-2.23)</td>
<td>0.76 (0.29-2.05)</td>
<td>.59</td>
</tr>
<tr>
<td>All-cause + ICD shock</td>
<td>1.32 (0.97-1.80)</td>
<td>0.96 (0.63-1.45)</td>
<td>.86</td>
</tr>
<tr>
<td>All-cause + VT/VF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; ICD, implantable cardioverter-deﬁbrillator; VT, ventricular tachycardia; VF, ventricular fibrillation.

Adequate control of potential confounders is essential to any cohort study where differences in patient dis-
ease severity often exist. In this cohort, patients who received ICDs were sicker at baseline than those who did
not. Those who received ICDs were likely to have higher rates of total and sudden cardiac death, since decisions
to implant were based on a positive EPS result, an ab-
normal Holter finding, and a prolonged QRS duration
greater than 120 milliseconds, all of which were found
to occur at higher frequencies in the ICD group. More-
over, ICD patients were more likely to have had lower
baseline LVEF, a nonnegative MTWA study, and a his-
tory of symptomatic heart failure, all of which were sig-
nificant predictors in our final Cox model for all-cause mortality (Table 3). Although ICD patients also had higher
utilization rates than non-ICD patients for β-blockers,
spirolonactone, statins, and digoxin, use of these medi-
cations did not significantly predict all-cause mortality
in our final Cox model. After adjustment for these base-
line differences between the patient groups, we found that
ICDs were associated with a significant reduction in total
mortality, primarily mediated through prevention of ar-
rhythmic deaths. The good discrimination found with our
propensity score model (C-statistic of 0.81) and our re-

cognizing our ICD population had a positive EPS finding com-
pared with the 36% found with the ICD group in the
MADIT-II trial. Indeed, risk-adjusted arrhythmia-
related mortality in the non-ICD group was higher in our
study population (20% at 3 years) than in the MADIT-II
trial population (16% at 3 years). When only arrhythmia-
related mortality was considered, however, both the
MADIT-II trial (HR, 0.33) and our study (HR, 0.35) found
similar dramatic results with ICD therapy.

As with most prospective cohort studies, the major
limitation is that the treatment groups being compared
were not identical in disease severity. Multivariate analy-

tical practice. After adjustment for multiple risk factors,
ICD placement was associated with a 47% reduction in
all-cause mortality. The magnitude of this mortality ben-
efit was almost entirely mediated through prevention of
arrhythmic death, since cardiovascular nonarrhythmic
and noncardiovascular mortality were comparable be-
tween the 2 groups. Adding further validity to these find-
ings, there was no difference in ICD and non-ICD pa-
tients in the combined end point of all-cause mortality,
ICD shocks, or symptomatic ventricular arrhythmias,
which suggests that ICD patients had better outcomes
because ICD shocks protected subjects from sudden car-
diac death and that our propensity score analysis com-
pared patients with similar baseline mortality risk. These
results suggest that the mortality reduction benefits seen
in the MADIT-II and the ischemic SCD-HeFT trial popu-
lations can be successfully translated into routine prac-
tice without a substantial dilution of benefits.

ICDs were associated with a significant reduction in all-
cause mortality. The relative risk reduction (47%) for all-cause mor-
tality found with ICDs in our effectiveness study was
greater than that seen for the MADIT-II trial (31%) and
among ischemic patients in the SCD-HeFT trial (28%). A
higher risk of arrhythmic death in our study popula-

tory of symptomatic heart failure, all of which were sig-
nificant predictors in our final Cox model for all-cause mortality (Table 3). Although ICD patients also had higher
utilization rates than non-ICD patients for β-blockers,
spirolonactone, statins, and digoxin, use of these medi-
cations did not significantly predict all-cause mortality
in our final Cox model. After adjustment for these base-
line differences between the patient groups, we found that
ICDs were associated with a significant reduction in total
mortality, primarily mediated through prevention of ar-
rhythmic deaths. The good discrimination found with our
propensity score model (C-statistic of 0.81) and our re-

cognizing our ICD population had a positive EPS finding com-
pared with the 36% found with the ICD group in the
MADIT-II trial. Indeed, risk-adjusted arrhythmia-
related mortality in the non-ICD group was higher in our
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rhythms were not standardized. Therefore, our analyses with this combined end point should be interpreted as a sensitivity analysis only. Because our cohort included only patients in sinus rhythm, our results are not generalizable to the 8% to 15% of patients in atrial fibrillation or paced rhythms.1,2 Finally, our study evaluated the effectiveness of ICDs in a cohort with ischemic heart disease and left ventricular dysfunction and would not be generalizable to patients with nonischemic heart disease.

In conclusion, prophylactic placement of ICDs in routine clinical practice was associated with lower all-cause and arrhythmic rates of mortality in patients with ischemic heart disease and left ventricular dysfunction. These apparent benefits occurred despite excellent medication management, which suggests that the mortality reduction benefits found with ICDs in well-controlled primary prevention efficacy trials can be translated into routine practice without substantial dilution in benefit.

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Author Contributions: Dr Chan had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The mortality reduction benefits found with ICDs in well-controlled primary prevention efficacy trials can be translated into routine practice without substantial dilution in benefit. Dr Chan took responsibility for the integrity of the data and takes responsibility for the integrity of the data analysis.

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