Effectiveness of Implantable Defibrillators for Preventing Arrhythmic Events and Death
A Meta-Analysis

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OBJECTIVES
The aim of this study was to compare the effectiveness of the implantable cardioverter defibrillator (ICD) and medical strategies for prevention of arrhythmic events and death.

BACKGROUND
The ICD is a potential strategy to reduce mortality in patients at risk of sudden death. The MEDLINE, EMBASE, and Cochrane Library electronic databases were searched from January 1966 to April 2002. All published randomized controlled trials comparing ICD implantation with medical therapy were reviewed. Four independent reviewers extracted data on all-cause mortality, nonarrhythmic death, and arrhythmic death using a standardized protocol.

RESULTS
Nine studies including over 5,000 patients were synthesized using both fixed-effects and random-effects models. The primary and secondary prevention trials showed a significant benefit of the ICD with respect to arrhythmic death, with relative risks (RR) of 0.34 and 0.50, respectively (both p < 0.001). The mortality benefit of the ICD was entirely attributable to a reduction in arrhythmic death (all trials: p < 0.00001). Whereas the secondary prevention trials exhibited a robust decrease in all-cause ICD mortality (RR 0.75; p < 0.001), the pooled primary prevention trials demonstrated decreased all-cause ICD mortality (RR 0.66; p < 0.05) which was dependent on selected individual trials. The disparity in ICD-related mortality reductions in the primary prevention trials was related to variability in the incidence of arrhythmic death between individual studies.

CONCLUSIONS
Although the ICD decreases the risk of arrhythmic death, its impact on all-cause mortality is related to the underlying risk of arrhythmia-related death relative to competing causes. Given the cost of the device strategy, policies of targeted intervention based on the future risk of arrhythmia are warranted. (J Am Coll Cardiol 2003;41:1573–82) © 2003 by the American College of Cardiology Foundation

Strategies to improve survival from fatal cardiac arrhythmias and all-cause mortality in patients at risk of sudden arrhythmic death have included the use of antiarrhythmic drugs (AAD), the implantable cardioverter defibrillator (ICD), or both (1–4). An AAD strategy using amiodarone has been shown to have modest effects on overall survival when compared with placebo in patients with left ventricular (LV) dysfunction (5,6). Although meta-analyses of total mortality and sudden death prevention with amiodarone have demonstrated a 10% to 19% reduction of total mortality (7,8), the longer term potential for serious adverse effects may limit the practical usefulness of this therapy in patients at risk of arrhythmia (9,10).

The ICD strategy is appealing because of its ability to terminate ventricular arrhythmias reliably, to provide early defibrillation, and perhaps to decrease or eliminate the need for concomitant antiarrhythmic medications and their associated adverse effects. Observational studies have shown that the ICD provides a survival advantage over AAD in patients with symptomatic arrhythmias, particularly in patients with depressed LV function (11–13). However, the ICD is associated with substantial costs and, therefore, precise estimates of device effectiveness are required. The objective of this study was to compare the effectiveness of medical therapy with the ICD in patients who are at risk of future episodes of sudden arrhythmic death and to clarify the issue of competing risks by analysis of the mode of death.
defibrillation thresholds or mechanism of drug or device action and/or where the primary end point of interest was not mortality were excluded. 4) Outcome: at least one of the reported outcomes was all-cause mortality, cardiac death, arrhythmic mortality, or cardiac arrest. A QUOROM statement flow diagram (17) for included and excluded studies is shown in Figure 1.

Quality assessment and data abstraction. Quality assessment of potentially qualifying studies was performed independently by four reviewers (D.S.L., L.D.G., F.C.G., and P.P.L.). Criteria for quality assessment included: 1) blinding of randomization, 2) complete follow-up, and 3) blinding/objectivity of outcome measurement. Blinding of intervention was not used for quality assessment because the intervention was surgical. Outcomes of all-cause mortality, arrhythmic death, and nonarrhythmic death (when available) were abstracted independently from each included study. Any potential disagreement was to be arbitrated by two of the authors (J.V.T. and D.A.A.).

Statistical analysis. Analysis was performed using the Mantel-Haenszel method. Relative risk (RR) and risk difference (RD) with 95% confidence intervals (CI) using the fixed effects model were calculated for the primary/secondary prevention trials separately and for all the trials in the overall analysis. If a statistically significant reduction in the RD was found, the number needed to treat was calculated (18). Statistical heterogeneity between studies was identified using the chi-square statistic, and a p ≤ 0.10 was deemed statistically significant. If significant statistical heterogeneity was identified, a random effects analysis was performed. We performed an overall analysis including all randomized trials. However, we anticipated clinical heterogeneity which was addressed by the performance of separate analyses of primary and secondary prevention studies and selected sensitivity analyses. Adverse events are reported overall as weighted percentages. Fatal perioperative adverse events included deaths occurring up to 30 days after device implantation.

RESULTS

Search results. A total of 1,077 potentially relevant articles were screened, and 1,003 were excluded after examination of the title and abstract. Of the 74 articles retrieved for further examination, 51 were excluded for the following reasons: nonrandomized (41 articles), absence of ICD arm (2 articles), quality of life outcome (1 article), no useful outcomes (6 articles), and protocol of ongoing study (1 article). Of the remaining 23 articles, a number were publications that evaluated the mode of death in the same patient sample as the primary study publication. There were 16 discrete randomized trials that were subsequently assessed for quality.

Details of the included study designs and trial interventions are shown in Table 1 (19–27). In total, the meta-
analysis represented a composite of over 5,000 patients. These studies were multicenter randomized trials spanning several countries (U.S., Canada, Netherlands, Australia, and Germany). Five trials were primary prevention studies. The primary prevention trials identified patients with poor LV function (LVEF ≤ 0.40) who were deemed to be at increased risk of sudden death (Fig. 2). Four randomized trials were secondary prevention studies that evaluated patients resuscitated from sudden cardiac death or with symptomatic ventricular tachyarrhythmias and reduced ejection fraction (Fig. 2).

Outcomes. Follow-up was nearly complete in these studies with fewer than 1.5% lost to follow-up in all studies. The average duration of follow-up was 18 to 20 months in the Antiarrhythmics Versus Implantable Defibrillators (AVID) study and the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) and ranged from 27 to 39 months in MADIT I, the Coronary Artery Bypass Graft Patch Trial (CABG Patch), the Canadian Implantable Defibrillator Study (CIDS), and the Multicenter Unsustained Tachycardia Trial (MUSTT). The Cardiac Arrest Study Hamburg (CASH) and the Cardiomyopathy Trial (CAT) had the longest follow-up durations: 57 to 66 months. In aggregate, there were a total of 1,292 deaths in 5,153 patients—primary prevention (n = 3,130) and secondary prevention (n = 2,023).

Primary prevention trials. The MADIT I and MUSTT studies showed significant reductions in arrhythmic death of 75% and 73%, respectively. In CABG Patch, there was a trend to decreased risk of arrhythmic death with the ICD; however, the CI crossed unity (RR 0.55; 95% CI 0.30 to 1.01). When the results were pooled, there was no statistical heterogeneity (p = 0.21), and a significant pooled reduction in arrhythmic death favoring the ICD (RR 0.34; 95% CI 0.23 to 0.50) was found (p < 0.00001). There was no excess of nonarrhythmic deaths in the ICD group with a pooled RR of 0.95 (95% CI 0.74 to 1.21) for this end point. For the end point of all-cause mortality, MUSTT, MADIT I, and MADIT II found significant reductions in all-cause death with relative risks in risk ranging from 29% to 59% (absolute risk reduction 26%, 23%, and 6%, respectively). The pooled data (Fig. 3) showed significant benefits in favor of the ICD with a RR reduction of death from any cause of 34% (p = 0.03). The random effects 95% CI of the RR reduction was 4% to 54%.

Secondary prevention. Individually, both AVID and CASH demonstrated statistically significant reductions in arrhythmic death with the ICD, with reported RR of 0.44
<table>
<thead>
<tr>
<th>Randomized Trials</th>
<th>Design/Sites</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>ICD Industry Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID (19)</td>
<td>Multicenter RCT with amiodarone or sotalol as medical therapy (U.S., Canada)</td>
<td>1,016 patients resuscitated from near-fatal VT/VF, sustained VT with syncope, or sustained VT with LVEF ≤ 0.40 and symptoms</td>
<td>507 randomized to ICD (472 transvenous, 25 thoracotomy, 10 not implanted). 509 randomized to AAD, 475 discharged on amiodarone</td>
<td>Early termination. Mode of death assessment by blinded independent events committee using internal criteria</td>
<td>None specified</td>
</tr>
<tr>
<td>CABG Patch (20)</td>
<td>Multicenter RCT with no antiarrhythmic drugs as conventional therapy (U.S., Germany)</td>
<td>1,055 patients undergoing CABG with LVEF ≥ 0.35 and abnormal signal-averaged ECG with no previous sustained VT/VF</td>
<td>446 randomized to ICD (434 implants occurred). 454 randomized to usual care; no protocol-driven AAD therapy instituted</td>
<td>Mode of death quality review and external events committee using the modified Hinkle and Thaler method</td>
<td>Guidant (unspecified type)</td>
</tr>
<tr>
<td>CASH (21)</td>
<td>Multicenter RCT with amiodarone or metoprolol as conventional therapy (Germany)</td>
<td>288 patients resuscitated from cardiac arrest due to sustained ventricular arrhythmia</td>
<td>99 randomized to ICD (44 transvenous, 55 thoracotomy). 92 randomized to amiodarone and 97 to metoprolol. Initial propafenone arm discontinued due to excess mortality</td>
<td>Internal criteria for sudden arrhythmic death</td>
<td>Guidant (Ventak AID/AICD/P/PRx/Mini)</td>
</tr>
<tr>
<td>CAT (22)</td>
<td>Multicenter RCT with standard medical therapy (no protocol-driven antiarrhythmics) as conventional therapy (Germany)</td>
<td>104 patients with dilated cardiomyopathy and LVEF ≤ 0.30</td>
<td>50 randomized to ICD (transvenous). 54 randomized to control</td>
<td>Internal criteria for sudden death</td>
<td>Guidant (Endotak, Ventak P2/P3/Px II/CPI)</td>
</tr>
<tr>
<td>CIDS (23)</td>
<td>Multicenter RCT with amiodarone as conventional therapy (Canada, Australia, U.S.)</td>
<td>659 patients with documented VF, out-of-hospital cardiac arrest requiring defibrillation, VT with syncope, VT with rate ≥150/min causing presyncope or angina in patient with LVEF ≤ 0.35, or syncope with VT inducible at EPS</td>
<td>328 randomized to ICD (277 transvenous, 33 thoracotomy, 18 did not receive ICD). 331 randomized to amiodarone</td>
<td>Death classification by the method of Hinkle and Thaler, adjudicated by a blinded external events validation committee</td>
<td>None specified</td>
</tr>
<tr>
<td>MADIT I (24)</td>
<td>Multicenter RCT with antiarrhythmic drugs as conventional therapy (U.S., Europe)</td>
<td>196 patients with MI ≥ 3 weeks before entry and asymptomatic unsustained VT unrelated to an acute MI and LVEF ≤ 0.35, with inducible VT not suppressed after intravenous procainamide</td>
<td>95 randomized to ICD (50 transvenous, 45 transthoracic, 5 did not undergo device implantation). 101 randomized to AAD (primarily amiodarone)</td>
<td>Early termination. Death classification by end point committee using Hinkle and Thaler method</td>
<td>Guidant (unspecified type)</td>
</tr>
<tr>
<td>MADIT II (25)</td>
<td>Multicenter RCT with standard medical therapy (no protocol-driven antiarrhythmics) as conventional therapy (U.S., Europe)</td>
<td>1,232 patients with MI ≥ 4 weeks before entry and LVEF ≤ 0.30</td>
<td>742 randomized to ICD (721 transvenous, 21 did not undergo device implantation). 490 randomized to conventional therapy</td>
<td>Early termination. Death classification by end point review committee</td>
<td>Guidant (unspecified type)</td>
</tr>
</tbody>
</table>

Continued on next page
Table 1 Continued

<table>
<thead>
<tr>
<th>Randomized Trials</th>
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<th>Participants</th>
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<th>ICD Industry Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTT (26)</td>
<td>Multicenter RCT with electrophysiologically guided antiarrhythmic therapy and no antiarrhythmics and conventional therapy (Canada, U.S.)</td>
<td>704 patients with coronary artery disease and unsustained VT and LVEF ≤ 0.40, with inducible VT at EPS</td>
<td>161 assigned to ICD and 190 non-ICD among patients randomized to EPS-guided antiarrhythmic therapy (class I agents, amiodarone, sotalol). 353 randomized to no antiarrhythmic therapy</td>
<td>Death classification by event committee using modified Hinkle-Thaler method</td>
<td>Bard, Guidant, Medtronic, St. Jude</td>
</tr>
<tr>
<td>Weaver et al. (27)</td>
<td>Multicenter RCT with antiarrhythmic drugs as conventional therapy (Netherlands)</td>
<td>60 patients with previous MI and resuscitated cardiac arrest due to VT or VF. VT inducibility during EPS and arrhythmia recurrence at ≥4 weeks post-MI were required</td>
<td>29 randomized to early ICD and 31 randomized to EPS-guided antiarrhythmic drug therapy</td>
<td>Internal death classification method</td>
<td>Guidant (Ventak P, Endotak)</td>
</tr>
</tbody>
</table>

AAD = antiarrhythmic drugs; AVID = Antiarhythmics Versus Implantable Defibrillators study; CABG = coronary artery bypass graft surgery; CABG Patch = Coronary Artery Bypass Graft Patch trial; CASH = Cardiac Arrest Study Hamburg; CAT = Cardiomyopathy Trial; CIDS = Canadian Implantable Defibrillator Study; ECG = electrocardiogram; EPS = electrophysiologic study; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter Unsustained Tachycardia Trial; RCT = randomized control trial; VF = ventricular fibrillation; VT = ventricular tachycardia.

The effect of industry versus non-industry sponsorship was independently shown to have a tendency to decreased arrhythmic death with an ICD, with RR of 0.70 and 0.27, respectively. When the studies were pooled (heterogeneity chi-square 3.6, p = 0.05), there was a 57% reduction (95% CI 34% to 62%) in arrhythmic death with the defibrillator (p = 0.0001). The absolute risk of death from any cause of 0.53 (95% CI 0.37 to 0.76; p = 0.00001) was reduced by 10% (95% CI 4% to 16%). There was only one trial in nonischemic patients, therefore pooling was not possible. The absolute risk in death from any cause was reduced by 10% (95% CI 4% to 16%). The findings was influenced by the heterogeneity of the results. Overall, there was a 5% (95% CI 1% to 11%) number needed to treat: 17. The absolute reduction in the risk of all-cause death, with a 30% reduction in the risk of arrhythmic death overall (random effects: p = 0.18). There was a 42% reduction in death overall (random effects: p = 0.0001). The RR of nonarrhythmic death from all trials combined was 0.75 (95% CI 0.64 to 0.87). The overall analysis (all trials). When all trials reporting arrhythmic deaths were included (Fig. 5), there was consistent evidence for the efficacy of the ICD in secondary prevention. The benefit of the ICD was robust in sensitivity analysis and not heavily influenced by any of the trials individually (Table 2).
explored in a separate analysis. There were seven trials supported by grants from ICD manufacturers, and pooling these trials showed a 33% RR reduction (p = 0.01). Of the two trials without such industry support, the results remained in favor of the defibrillator with a 25% reduction in risk (p = 0.001). Sensitivity analysis, excluding MADIT I and II, still demonstrated significant benefit in favor of the defibrillator for all-cause mortality (RR 0.73, 95% CI 0.57

<table>
<thead>
<tr>
<th>Study</th>
<th>Defibrillator n/N</th>
<th>Conventional n/N</th>
<th>RR (95% CI Random)</th>
<th>Weight %</th>
<th>RR (95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT 1996</td>
<td>15/95</td>
<td>39/101</td>
<td>0.41[0.24,0.69]</td>
<td>17.0</td>
<td>0.41[0.24,0.69]</td>
</tr>
<tr>
<td>CABG Patch 1997</td>
<td>102/446</td>
<td>96/454</td>
<td>1.08[0.85,1.38]</td>
<td>23.0</td>
<td>1.08[0.85,1.38]</td>
</tr>
<tr>
<td>MUSTT 1999</td>
<td>35/161</td>
<td>255/537</td>
<td>0.46[0.34,0.62]</td>
<td>21.8</td>
<td>0.46[0.34,0.62]</td>
</tr>
<tr>
<td>CAT 2002</td>
<td>13/50</td>
<td>17/54</td>
<td>0.83[0.45,1.52]</td>
<td>15.2</td>
<td>0.83[0.45,1.52]</td>
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<tr>
<td>MADIT II 2002</td>
<td>105/742</td>
<td>97/490</td>
<td>0.71[0.56,0.92]</td>
<td>22.9</td>
<td>0.71[0.56,0.92]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>270/1494</td>
<td>504/1636</td>
<td>0.66[0.46,0.96]</td>
<td>100.0</td>
<td>0.66[0.46,0.96]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=23.69 df=4 p=0.0001
Test for overall effect z=-2.15 p=0.03
to 0.94; \( p = 0.01 \) and arrhythmic death (RR 0.44, 95% CI 0.35 to 0.56; \( p < 0.001 \)). Finally, when MUSTT was excluded from the pooled analysis of primary prevention trials, the impact of the ICD on arrhythmic death remained significant with a RR of 0.45 (95% CI 0.26 to 0.78; \( p < 0.01 \)). However, the reduction in risk of all-cause mortality (RR 0.74; 95% CI 0.51 to 1.08) was no longer significant (\( p = 0.12 \)).

**Treatment-related complications.** Perioperative death complicating defibrillator implantation occurred in 1.2% without concomitant thoracotomy and coronary artery bypass grafting; however, such deaths occurred in 5.5% of patients in CABG Patch. Other commonly reported adverse events (and weighted percentages) in the defibrillator arm were infection (2.4%), hematoma or seroma (3.7%), pericardial effusion or tamponade (0.6%), pneumothorax (1.6%), lead dislodgement or fracture (2.3%), and device malfunction (2.0%). Among the medical arms employing antiarrhythmic agents, amiodarone pulmonary toxicity was the most often reported adverse effect, occurring in 3.0% to 5.7% (weighted mean 4.8%) of patients by study termination.

**DISCUSSION**

Our meta-analysis demonstrated a significant survival advantage with the defibrillator for patients at risk of sudden cardiac death. Pooling primary and secondary prevention studies together, defibrillators were associated with a 57% reduction in the risk of an arrhythmic death and a 30% decrease in risk of all-cause mortality as compared with medical therapy alone. When distinguishing primary from secondary prevention studies, only the latter was associated with a consistent reduction in total mortality. In contrast, the impact of defibrillators on total mortality for primary prevention was variable and heavily dependent on the patient population examined. Notwithstanding the differential effect on total mortality, both primary and secondary prevention trials were associated with a similar reduction in the risk of arrhythmic death.

**Implantable defibrillator and survival benefits.** The effects of the ICD on outcomes in secondary prevention were consistent with other investigators (28). Specifically, the ICD was associated with a 50% RR reduction for arrhythmic death and a 25% RR reduction for all-cause mortality (both absolute risk reductions, 7%). The secondary prevention trial results were robust and consistent from study to study.

To our knowledge, ours is the first meta-analysis evaluating the efficacy of defibrillators in primary prevention of sudden cardiac death reporting random effects analyses in the presence of between-study heterogeneity. Primary prevention studies showed a variable effect on all-cause mortality. A factor that may have contributed to the variability
in primary prevention studies may have been the underlying cardiac substrate. Whereas the majority of primary prevention studies included patients with ischemic heart disease, CAT was the only trial that included exclusively patients with nonischemic cardiomyopathy. The role of defibrillators in the latter group may be clarified by trials that address this subpopulation of patients with LV dysfunction. Yet, the effect of prophylactic defibrillators on arrhythmic death in the primary prevention population was surprisingly similar and consistent with its risk reduction for arrhythmic death in secondary prevention. Excluding the MUSTT trial, a primary prevention study for which the ICD was arguably based on selection rather than on randomization, the ICD was associated with RR reductions of 50% and 45% for arrhythmic death among the secondary and primary prevention trials, respectively. Given that defibrillators do not reduce the risk of nonarrhythmic death, the difference between the ICD outcome effects for primary prevention and secondary prevention relates to the baseline risk of life-threatening arrhythmia. In short, the attenuated and inconsistent effect of defibrillators on total mortality among primary prevention patients directly reflects a more heterogeneous spectrum of risk for life-threatening arrhythmias in the months and years that follow.

Risk stratification. If ultimately, the clinical effectiveness (and economic impact) of the ICD reflects the baseline risk of arrhythmic death in the population, it is incumbent upon researchers and clinicians to stratify patients in accordance with the risk of life-threatening arrhythmias. Our analysis crudely stratified patients into those with and without previous cardiac arrest or symptomatic ventricular tachycardia. Arguably, this is the simplest form of risk stratification. However, available evidence suggests that within each subgroup, the baseline risk of a life-threatening arrhythmia impacts upon the subsequent effectiveness of defibrillators on total mortality. For example, within a secondary prevention trial, a further high-risk subset included those with the lowest ejection fractions (29,30). In addition to underlying ejection fraction and previous history of cardiac arrest, other important case-mix and clinical factors may predict the risk of life-threatening arrhythmic complications; these include age (30), functional status (30), the etiology of cardiac disease (2,31), residual ischemic burden (32–35), electrocardiographic indices (36–38), and inducibility of arrhythmias at electrophysiologic study (39–41). The incremental importance of other strategies that delineate and/or modify the risk of life-threatening complications (e.g., electrophysiologic study, revascularization) requires further evaluation. We believe that the magnitude of absolute survival benefit and the cost-effectiveness of the ICD will depend on the efficiency by which patients who are at high risk of arrhythmic death can be identified in the population (42).

The methodology employed for stratification of risk of arrhythmic death in future studies might include predictive models or clinical decision aids from substudies of RCTs (30,43). Simple clinical rules, such as those gleaned from electrocardiographic analysis, may be clinically useful. Ultimately, no single test may be highly predictive, and it may require a combination of predictive tests to identify a

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**Table 1.** Impact of the randomized defibrillator trials on arrhythmic death. For each randomized trial, the number of arrhythmic deaths (n) and the number assigned (N) are shown. All studies showed consistent benefit in reducing arrhythmic death with the implantable cardioverter defibrillator (ICD), and there was no statistical heterogeneity between studies (p = 0.18). Over all studies reporting arrhythmic deaths, the defibrillator reduced the risk of arrhythmic death significantly (pooled relative risk 0.43; 95% CI 0.35 to 0.54). The ICD effect was a highly significant reduction in risk of arrhythmic death (p < 0.00001). The horizontal tips of the black diamond represent the 95% CI, and the midpoint of the diamond represents the point estimate of the RR. CABG Patch = Coronary Artery Bypass Graft Patch Trial; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MUSTT = Multicenter Unsustained Tachycardia Trial. Other abbreviations as in Figure 4.

<table>
<thead>
<tr>
<th>Study</th>
<th>Defibrillator n/N</th>
<th>Conventional n/N</th>
<th>RR (95% CI Fixed)</th>
<th>Weight %</th>
<th>RR (95% CI Fixed)</th>
</tr>
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<tr>
<td>Wever 1995</td>
<td>1/29</td>
<td>4/31</td>
<td></td>
<td>1.5</td>
<td>0.27[0.03,0.25]</td>
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<td>MADIT 1996</td>
<td>3/95</td>
<td>13/101</td>
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<td>5.0</td>
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<td>AVID 1997</td>
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<td>55/509</td>
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<td>21.8</td>
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<td>MUSTT 1999</td>
<td>12/161</td>
<td>146/537</td>
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<td>26.7</td>
<td>0.27[0.16,0.48]</td>
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<td>Total (95% CI)</td>
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<td>351/2152</td>
<td></td>
<td>100.0</td>
<td>0.43[0.35,0.54]</td>
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</table>

Test for heterogeneity chi-square=8.86 df=6 p=0.18
Test for overall effect z=-7.33 p<0.00001

**Figure 5.** Impact of the randomized defibrillator trials on arrhythmic death. For each randomized trial, the number of arrhythmic deaths (n) and the number assigned (N) are shown. All studies showed consistent benefit in reducing arrhythmic death with the implantable cardioverter defibrillator (ICD), and there was no statistical heterogeneity between studies (p = 0.18). Over all studies reporting arrhythmic deaths, the defibrillator reduced the risk of arrhythmic death significantly (pooled relative risk 0.43; 95% CI 0.35 to 0.54). The ICD effect was a highly significant reduction in risk of arrhythmic death (p < 0.00001). The horizontal tips of the black diamond represent the 95% CI, and the midpoint of the diamond represents the point estimate of the RR. CABG Patch = Coronary Artery Bypass Graft Patch Trial; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MUSTT = Multicenter Unsustained Tachycardia Trial. Other abbreviations as in Figure 4.
high-risk subset (44). In addition to the need for further study of the prognostic value of diagnostic tests, equally important may be the consideration of patient-related factors. This includes consideration of the cardiac substrate and comorbidities. Factors that predict high utility of the ICD in patients with ischemic heart disease may not apply to those with nonischemic cardiomyopathy. In addition, noncardiac comorbidities may lead to mechanisms of death for which the ICD would not change the disease history and the ultimate prognosis of the patient. This concept of competing risks may diminish the effectiveness of the defibrillator on all-cause mortality (45). Studies that include competing risks may further improve the reliability of the primary prevention trials. For example, we had only one trial in nonischemic cardiomyopathy, which may complement our primary prevention analysis of patients with coronary artery disease. Additional randomized trials of ICD strategies in patients with coronary artery disease will help to increase further the precision of the estimated benefits of the defibrillator and may lead to greater robustness of our results. A number of pending publications of randomized trials, including Amiodarone Versus Implantable Defibrillator in Patients with Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT), Beta-blocker Strategy plus Implantable Cardioverter Defibrillator Trial (BEST–ICD), Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE), Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), and Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT), may further improve the reliability of the primary prevention estimates of ICD effect. Second, there may be other reasons for statistical and clinical heterogeneity that could not be realized from this analysis, such as the effects of variable follow-up times. An analysis of pooled survival time data may yield further insights. Third, studies with arrhythmic death end points are limited by the accuracy of death classification methods, and the further subclassification of arrhythmic deaths as bradyarrhythmic or tachyarrhythmic deaths may be limited without studies employing combined ventricular pacemaker and defibrillator. Fourth, no cost-effectiveness analysis was undertaken. Nonetheless, the robust estimates of event rates as determined by our study may set the stage for future ICD cost–benefit analysis.

Conclusions. The defibrillator is highly effective in reducing the risk of arrhythmic death when used in either a primary or secondary prevention context. Pooled analysis of all-cause mortality showed a reduction in risk of death with defibrillator implantation. While the secondary prevention results were robust, primary prevention findings were sensitive to the contributions of individual trials. Given the fiscal implications of the primary prevention trials, we believe that the impact of device implantation strategies on health policy, cost-effectiveness, and access to this form of therapy should be further evaluated. Our results suggest that net survival benefits and cost-effectiveness of the ICD when applied to the population will depend upon efficient use of devices for those at highest risk of life-threatening arrhythmias.

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REFERENCES
33. Exner DV, Klein GJ, Prystowsky EN. Primary prevention of sudden death with implantable defibrillator therapy in patients with cardiac disease: can we afford to do it? (can we afford not to?). Circulation 2001;104:1564–70.