Implantable Cardioverter-Defibrillators
Expanding Indications and Technologies

Zachary Goldberger, MD
Rachel Lampert, MD

SUDDEN CARDIAC DEATH (SCD) causes approximately 450 000 deaths annually in the United States and nearly 50% of all cardiovascular mortality worldwide.1-3 Ventricular tachycardia degenerating into ventricular fibrillation causes two thirds of SCD.4-6 Because there are no warning symptoms to identify persons who might potentially experience SCD,7 successful therapy has focused on identifying high-risk patients and treating them with implantable cardioverter-defibrillators (ICDs), which continuously monitor the heart rhythm and deliver a shock or other appropriate electrical therapy on detection of a potentially fatal sustained ventricular arrhythmia.7 This review will highlight the evolving indications for the ICD and describe technological advances in defibrillator therapy, emphasizing the major clinical trials demonstrating the efficacy of the device in primary and secondary prophylaxis of SCD.

EVIDENCE ACQUISITION

We conducted a literature search using the Pubmed and MEDLINE databases from January 1996 to July 2005, using the Medical Subject Heading implantable defibrillator, limited to randomized controlled trials (RCTs) reported in English. Abstracts were reviewed to identify those that included an ICD and a non-ICD group and that had primary outcomes of all-cause mortality, cardiac death, and/or arrhythmic mortality. We performed a similar search to identify RCTs of cardiac resynchronization therapy (CRT) including a CRT and a non-CRT group (including both mortality and other end points). A total of 22 trials were identified. Scientific statements and guidelines from official societies (eg, the American College of Cardiology [ACC], American Heart Association [AHA], and the Heart Rhythm Society) were also reviewed.

Context Sudden cardiac death (SCD) is a major challenge facing contemporary cardiology. For an increasing number of patients, the current standard of care for the treatment and prevention of SCD is the implantable cardioverter-defibrillator (ICD). Since its introduction, there have been numerous advances in ICD technology, and indications for its use have expanded greatly in the past year.

Objective To highlight the evolving indications for and the numerous advances in ICD technology, with emphasis on primary and secondary prophylaxis of SCD.

Evidence Acquisition Electronic literature search of the Pubmed and MEDLINE databases from January 1996 to July 2005, using the Medical Subject Heading implantable defibrillator. Abstracts and titles were reviewed to identify English-language randomized controlled trials that included an ICD group and a non-ICD group and that had end points of all-cause mortality, cardiac death, and/or arrhythmic mortality as the main outcome. A further MEDLINE search was conducted to identify randomized controlled trials of cardiac resynchronization therapy (CRT) with a CRT and a non-CRT group (including both mortality and other end points). Other studies were included that clarify aspects of device function and other relevant issues. A total of 22 trials were identified.

Evidence Synthesis ICD implantation improves survival in patients with a history of life-threatening ventricular arrhythmia. More recent evidence shows that ICD implantation also improves survival as primary prophylaxis against SCD in patients at high risk for ventricular arrhythmias, including those with left ventricular ejection fraction (LVEF) of 35% or less and New York Heart Association class II or III heart failure and those with a history of myocardial infarction and LVEF of 30% or less. Cardiac resynchronization improves symptoms, quality of life, and survival for patients with advanced heart failure and intraventricular conduction delays and ventricular dyssynchrony.

Conclusions ICDs have been shown to improve survival as both primary and secondary prophylaxis in an expanding population of patients. Ongoing ICD research may continue to delineate groups with survival benefit from ICDs, and the use and indications of these devices in clinical practice will continue to expand.

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Author Affiliations: Department of Medicine, University of Washington Medical Center, Seattle (Dr Goldberger) and Department of Medicine, Yale University School of Medicine, New Haven, Conn (Dr Lampert).

Corresponding Author: Rachel Lampert, MD, Section of Cardiology, Yale University School of Medicine, 333 Cedar St, FMP 3, New Haven, CT 06520 (rachel.lampert@yale.edu).

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EVIDENCE SYNTHESIS
Expanding Indications
The introduction of the ICD into clinical practice has been an evolving process. While secondary prophylaxis for patients surviving a life-threatening ventricular arrhythmia has long been the standard of care, more recent trials also demonstrate the survival benefit of the ICD in expanding groups of patients at high risk (ie, primary prophylaxis).

Secondary Prevention Trials
Several trials have investigated the role of the ICD in secondary prevention of SCD (TABLE 1).8-12 The largest include the Antiarrhythmics vs Implantable Defibrillators (AVID) trial,8 the Cardiac Arrest Study Hamburg (CASH),9 and the Canadian Implantable Defibrillator Study (CIDS).10 Each trial randomly assigned patients to receive ICD vs pharmacological therapy, and in each, the ICD reduced total mortality, although only the AVID results reached statistical significance.

AVID was also the largest and best-designed trial, including nearly exclusive use of transvenous defibrillators and comparing the ICD against the best available antiarrhythmic drug therapy (amiodarone and sotalol), unlike CASH and CIDS. Further, a meta-analysis of the 3 trials confirmed that ICD therapy resulted in significant relative reductions in total mortality (27%) and arrhythmic mortality (51%).13 Use of the ICD improved survival regardless of underlying structural heart disease, β-blockade, surgical revascularization, or presenting arrhythmia (ventricular tachycardia/fibrillation). Patients with the lowest left ventricular ejection fraction (LVEF) and those with advanced congestive heart failure (CHF) benefited most.13 Interestingly, the AVID registry, enrolling patients not qualifying for randomization, showed that some groups previously considered at lower risk for SCD—ie, patients with hemodynamically stable ventricular tachycardia or arrhythmias attributed to “reversible causes”—actually had significantly worse survival than patients randomly assigned to receive ICD, suggesting that these groups may also benefit from ICDs.14

Table 1. Secondary Prevention of Sudden Cardiac Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>No.</th>
<th>Population</th>
<th>Mean Follow-up, mo</th>
<th>Main Findings</th>
</tr>
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<tbody>
<tr>
<td>AVID,8 1997</td>
<td>Antiarrhythmic medications (97% amiodarone, 5% sotalol) vs ICD</td>
<td>1016</td>
<td>Survived VT/VF/cardiac arrest; VT with syncope; VT with LVEF ≤40%</td>
<td>18</td>
<td>Reduction in total mortality with ICD therapy (HR, 0.69; 95% CI, 0.51-0.85; P &lt; .02)</td>
</tr>
<tr>
<td>CASH,9 2000</td>
<td>Antiarrhythmic medications propafenone (withdrawn early), metoprolol, or amiodarone vs ICD</td>
<td>288</td>
<td>Survived VT/VF/cardiac arrest</td>
<td>57</td>
<td>Reduction in total mortality with ICD therapy (HR, 0.82; 95% CI, 0.60-1.11; P = .08)*</td>
</tr>
<tr>
<td>CIDS,10 2000</td>
<td>Amiodarone vs ICD</td>
<td>659</td>
<td>Survived VT/VF/cardiac arrest; VT with syncope; VT with LVEF ≤35% and cycle length ≤400 ms</td>
<td>35</td>
<td>Reduction in death from any cause with ICD therapy (P = .14)</td>
</tr>
<tr>
<td>DEBUT,11 2003</td>
<td>β-Blocker vs ICD</td>
<td>86</td>
<td>Survived VT/VF/cardiac arrest; no structural abnormalities</td>
<td>36</td>
<td>Total of 7 deaths, all of which occurred in the β-blocker group (3 deaths during 2-y follow-up, P = .07; 4 deaths during 3-y follow-up, P = .02)</td>
</tr>
<tr>
<td>MAVERIC,12 2004</td>
<td>Electrophysiologically guided therapy (antiarrhythmic, revascularization, or ICD) vs amiodarone</td>
<td>214</td>
<td>Survived VT/VF/cardiac arrest</td>
<td>60‡</td>
<td>Lower mortality with ICD therapy vs non-ICD therapy (HR, 0.54; 95% CI, 0.39-0.97; P = .046)</td>
</tr>
</tbody>
</table>

Abbreviations: AVID, Antiarrhythmics vs Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CI, confidence interval; CIDS, Canadian Implantable Defibrillator Study; DEBUT, Defibrillator vs β-Blockers for Unexplained Death in Thailand; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MAVERIC, Midlands Trial of Empirical Amiodarone vs Electrophysiologic-Guided Intervention and Cardioverter Implant in Ventricular Arrhythmias; NNT, number needed to treat; VT, ventricular fibrillation; VT with syncope; VF, ventricular tachycardia.

*No advantage to electrophysiologic testing.
†Median follow-up.
‡Data not available for calculation of NNT.

Primary Prevention Trials
The dismal survival rate after cardiac arrest15-17 provides strong impetus to identify high-risk patients who might benefit from an ICD before a first life-threatening arrhythmia. Historically, patients with left ventricular dysfunction after myocardial infarction (MI) and a history of nonsustained ventricular tachycardia underwent electrophysiologic testing to identify those believed to be at highest risk, ie, those with inducible, nonsuppressible, ventricular tachyarrhythmias.18,19 This population was the target for the first primary prevention trials (TABLE 2). The Multicenter Automatic Defibrillator Trial (MADIT)20 compared ICDs with conventional therapy (mainly amiodarone, LVEF ≤35%), and the Multicenter Unsustained Tachycardia Trial (MUSTT)21 compared electrophysiologically guided therapy (ICDs or drug therapy) with no guided therapy (LVEF ≤40%).

MADIT was prematurely aborted after enrolling only 196 patients when preliminary analysis revealed a dra-
mantic benefit of ICD therapy in reducing overall mortality by 54% \( (P = .009) \). MADIT had no control group, raising the question of whether the trial proved benefit of ICD or detriment of amiodarone. In addition, use of \( \beta \)-blockers was higher in the ICD group. However, MUSTT, while not designed to evaluate the ICD, supported the MADIT findings. The original hypothesis of MUSTT was that electrophysiologically guided therapy, either pharmacological or device-based, could reduce arrhythmic and total mortality in high-risk patients who had arrhythmias induced at electrophysiologic study. In patients randomized to receive electrophysiologically guided therapy, antiarrhythmic drugs were tested first, and, at the physician’s discretion, nonresponders received ICDs. MUSTT did show a decrease in arrhythmic death/cardiac arrest with electrophysiologically guided therapy, the investigators’ primary hypothesis. However, subgroup analysis revealed that the benefits were due entirely to the ICD: at 5 years, there were absolute reductions in total mortality of 31% when compared with those receiving pharmacological therapy and of 24% when compared with those receiving no therapy (24% mortality in the ICD group, 55% in the pharmacological therapy group, and 48% in the group receiving no therapy).

In MUSTT, few patients received amiodarone, and ICD use was not randomized. However, taken together, MUSTT and MADIT clearly demonstrate the benefit of the ICD in the population of patients with coronary artery disease, low LVEF, and inducible ventricular arrhythmia.

The MUSTT registry also followed up patients who had clinical criteria for the trial but no inducible arrhythmias. Surprisingly, while 5-year mortality for these patients was statistically lower than for inducible patients randomly assigned to receive no therapy (44% and 48%, respectively; \( P = .005 \)), it was significantly higher than that for the inducible, ICD-treated patients (24%). These data implied that noninducible patients with left ventricular dysfunction and nonsustained ventricular tachycardia may also benefit from a prophylactic ICD, and that electrophysiologic study may be an inadequate stratifier of risk.

The second MADIT trial (MADIT II)\(^23\) directly addressed the value of prophylactic ICD implantation in patients with coronary artery disease and LVEF of 30% or less, without electrophysiologic risk stratification. Patients receiving the ICD showed a 31% relative reduction in mortality at any interval (\( P = .02 \)). Of note, among 593 patients in the ICD group who underwent peri-implant electrophysiologic testing (not an entry criterion), inducibility did not predict later ventricular arrhythmia, supporting a low sensitivity for electrophysiologic testing.

One concern following MADIT II was the higher rate of CHF in the ICD

<table>
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<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT,(^20) 1996</td>
<td>Antiarrhythmic therapy (74% amiodarone) vs ICD</td>
<td>196</td>
<td>Prior MI; LVEF ≤35%; asymptomatic NSVT; NYHA class I-II; inducible VT refractory to intravenous procainamide on electrophysiologic study</td>
<td>27</td>
<td>Reduction in total mortality with ICD therapy (HR, 0.46; 95% CI, 0.26-0.92; ( P = .009 )); NNT = 6 at 5 y</td>
</tr>
<tr>
<td>CABG-Patch,(^21) 1997</td>
<td>CABG surgery plus ICD vs CABG surgery plus conventional therapy</td>
<td>900</td>
<td>Patients scheduled for CABG; LVEF ≤35%; positive SAECG result</td>
<td>32</td>
<td>No reduction in total mortality with ICD therapy (HR, 1.07; 95% CI, 0.81-1.42; ( P = .64 ))</td>
</tr>
<tr>
<td>MUSTT,(^22) 1999</td>
<td>Electrophysiologically guided therapy (antiarrhythmic or ICD) vs conventional therapy</td>
<td>704</td>
<td>Prior MI; LVEF ≤40%; CAD; inducible VT on electrophysiologic study</td>
<td>39*</td>
<td>Reduction in total mortality with ICD therapy (HR, 0.69; 95% CI, 0.32-0.63; ( P &lt; .001 )); NNT = 3 at 5 y</td>
</tr>
<tr>
<td>MADIT II,(^23) 2002</td>
<td>Conventional therapy vs ICD</td>
<td>1232</td>
<td>Prior MI; LVEF ≤30%</td>
<td>20</td>
<td>Reduction in total mortality with ICD therapy (HR, 0.69; 95% CI, 0.51-0.93; ( P = .02 )); NNT = 18 over mean 20 mo</td>
</tr>
<tr>
<td>DINAMIT,(^24) 2004</td>
<td>Conventional therapy vs ICD</td>
<td>674</td>
<td>Recent MI (within 4-40 d), LVEF ≤35%; impaired cardiac autonomic modulation (heart rate variability)</td>
<td>39</td>
<td>No reduction in death from any cause with ICD therapy (( P = .66 )); Risk of arrhythmic death lower with ICD therapy (( P = .009 )); HR, 1.08; 95% CI, 0.76-1.55*</td>
</tr>
<tr>
<td>SCD-HeFT,(^25) 2005</td>
<td>Conventional therapy vs amiodarone vs ICD</td>
<td>2521</td>
<td>NYHA class II/III CHF (ischemic and nonischemic); LVEF ≤35%</td>
<td>45.5*</td>
<td>Overall: reduction in mortality with ICD therapy (( P = .007 )); Ischemic heart disease: reduction in mortality with ICD therapy (( P = .05 )); HR, 0.77; 97.5% CI, 0.62-0.96; NNT = 14 at 5 y</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; NNT, number needed to treat; SAECG, signal-averaged electrocardiogram; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VT, ventricular tachycardia.

*Median follow-up.

†NNT not appropriate, as ICD implantation resulted in nonsignificantly higher mortality.
group,\textsuperscript{23,27} The later Dual Chamber and VVI Implantable Defibrillator (DAVID) trial,\textsuperscript{28} which randomly assigned patients to receive either dual- or single-chamber ICDs, showed higher incidence of CHF with right ventricular pacing. The mechanism by which right ventricular pacing effectively causes iatrogenic left bundle-branch block and subsequent contractile dysynchrony likely explains the higher incidence of CHF in ICD-treated patients in MADIT II. This concern was not appreciated at that time. Based on these and other data showing deleterious effects of right ventricular pacing,\textsuperscript{29,30} devices are now programmed to minimize such pacing.\textsuperscript{31,32}

The recently published Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)\textsuperscript{25} enrolled patients with either ischemic or nonischemic cardiomyopathy, New York Heart Association (NYHA) class II or III heart failure, and LVEF less than or equal to 35%. The results confirmed the benefit of ICD in ischemic patients in MADIT II, as well as the findings of a previous smaller study of patients with nonischemic cardiomyopathy (TABLE 3).\textsuperscript{24,25,33-35} The Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy (DEFINITE) trial.\textsuperscript{35} In SCD-HeFT, ICD-treated patients lived longer than those treated with amiodarone (which had no benefit) or conventional medical therapy. While the concern has been raised that ICD benefit in MADIT II may have been skewed by the short follow-up,\textsuperscript{36} SCD-HeFT showed ICD benefit extending to 5 years, independent of heart failure etiology (ischemic vs nonischemic). Subgroup analysis revealed benefit in patients with NYHA class II, but not class III, heart failure. These studies suggest that most patients with LVEF less than or equal to 35% should receive an ICD (specifically those with NYHA class II or III heart failure, or class I with history of MI and LVEF ≤30%).

However, whether LVEF should now be the primary factor determining ICD eligibility remains controversial.\textsuperscript{37} In MUSTT, LVEF had poor specificity in predicting SCD;\textsuperscript{24} in other studies, combinations of factors were more predictive.\textsuperscript{39,40} Neither MADIT II nor SCD-HeFT evaluated ICD benefit in patients known to be noninducible. This may explain why the absolute reductions in all-cause mortality for MADIT II and SCD-HeFT (6% and 7%, respectively) are much smaller than for MADIT or MUSTT (23% and 31%, respectively), which included electrophysiologic criteria. There are correspondingly larger numbers needed to treat for SCD-HeFT/MADIT II (15-17) than for MUSTT/MADIT (3-4). Thus, the benefit of ICD therapy may be greater in patients with CHF risk beyond low LVEF (although these differences in absolute risk reduction may also be due to better medical therapy in the control groups in the later trials\textsuperscript{41}).

Editorialists have questioned the validity of ICD implantation in all post-MI patients with reduced LVEF.\textsuperscript{37,42,33} Suggesting that further risk stratification is still needed.\textsuperscript{37} The potential role for noninvasive risk-stratifiers such as T-wave alternans, shown to have good predictive value,\textsuperscript{44,45} remains undetermined.

Two studies showed no benefit of ICD for primary prophylaxis in specific populations: the Coronary Artery Bypass Graft Patch (CABG-Patch) trial\textsuperscript{41} and the Defibrillator in Acute Myocardial Infarction (DINAMIT) trial (Table 2).\textsuperscript{54} CABG-Patch randomly assigned patients with an abnormal signal-averaged electrocardiogram and scheduled for coronary

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<tbody>
<tr>
<td>CAT,\textsuperscript{23} 2002</td>
<td>Conventional therapy vs ICD</td>
<td>104</td>
<td>NYHA class II/III, NIDCM; LVEF ≤30%; asymptomatic NSVT</td>
<td>66</td>
<td>No reduction in total mortality with ICD therapy (P = .55)\textsuperscript{+}</td>
</tr>
<tr>
<td>AMIOVIRT,\textsuperscript{24} 2003</td>
<td>Amiodarone vs ICD</td>
<td>103</td>
<td>NYHA class I-II, NIDCM; LVEF ≤35%; asymptomatic NSVT</td>
<td>36</td>
<td>No reduction in total mortality with ICD therapy (P = .80)\textsuperscript{+}</td>
</tr>
<tr>
<td>DEFINITE,\textsuperscript{36} 2004</td>
<td>Conventional therapy vs ICD</td>
<td>458</td>
<td>NIDCM; LVEF ≤35%; NSVT or PVCs</td>
<td>29</td>
<td>Reduction in total mortality with ICD therapy (P = .08). Reduction in death from arrhythmia with ICD therapy (P = .006). HR, 0.65; 95% CI, 0.40-1.06.</td>
</tr>
<tr>
<td>SCD-HeFT,\textsuperscript{25} 2005</td>
<td>Conventional therapy vs amiodarone vs ICD</td>
<td>2521</td>
<td>NYHA class II/III CHF (ischemic and nonischemic); LVEF ≤35%</td>
<td>45.5\textsuperscript{±}</td>
<td>Overall: reduction in mortality with ICD therapy (P = .007). Nonischemic heart disease: reduction in mortality with ICD therapy (P = .06). HR, 0.77; 97.5% CI, 0.62-0.96. NNT = 14 at 5 y.</td>
</tr>
</tbody>
</table>

Abbreviations: AMIOVIRT, Amiodarone vs Implantable Defibrillator in Patients with Nonischemic Cardiomyopathy and Asymptomatic Non-sustained Ventricular Tachycardia; CAT, Cardiomyopathy Trial; CHF, congestive heart failure; CI, confidence interval; DEFINITE, Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; ICD therapy, left ventricular ejection fraction; NIDCM, nonischemic dilated cardiomyopathy; NNT, number needed to treat; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular contraction; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

HR and CI not reported.
NNT not calculated because of nonsignificant results.
Median follow-up.
artery bypass graft surgery to receive treatment with either an ICD implanted during surgery or no ICD. The ICD showed no benefit, likely due to the lower-risk profile of the patient population. First, while preoperative ejection fractions were low, they may have improved with surgery. Also, the signal-averaged electrocardiogram may lack specificity.\textsuperscript{18,19} Revascularization itself may have protected against arrhythmia, although in AVID, the ICD offered similar survival rates independent of revascularization.\textsuperscript{8}

A recent substudy of the large VALsartan in Acute Myocardial Infarction Trial (VALIANT)\textsuperscript{46} demonstrated that SCD risk is highest in the first 30 days after MI (complicated by reduced LVEF and/or CHF), suggesting that early ICD implantation might save lives. However, the DINAMIT study, which randomly assigned such patients to receive an ICD or conventional medical therapy, showed no ICD benefit early after MI, possibly due to the low event rate in this small study. It is also possible that the VALIANT patients with SCD were sicker than the survivors, with competing risks. DINAMIT supports this theory, as patients who received shocks were also more likely to die. It is unknown whether further risk stratification, or noninvasive measures such as a wearable external vest or an automatic external defibrillator, might be more beneficial and cost-effective early after MI.\textsuperscript{47}

Overall, these trials strongly support ICD implantation for secondary prevention in patients with prior life-threatening arrhythmia, and as primary prophylaxis for many patients with a low LVEF and coronary artery disease, CHF, or both. The ACC/AHA/North American Society for Pacing and Electrophysiology (now the Heart Rhythm Society) last revised their guidelines for ICD implantation in 2002.\textsuperscript{48} and, as such, these guidelines do not yet reflect the most recent primary prophylaxis trials. However, the 2005 ACC/AHA Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult\textsuperscript{49} recommend that “consideration of ICD implantation is recommended in patients with LVEF less than 30% and mild to moderate symptoms of heart failure and in whom survival with good functional capacity is otherwise anticipated to extend beyond 1 year.” In addition, the Centers for Medicare & Medicaid Services has expanded coverage for ICDs primarily based on the results of MADIT II and SCD-HeFT (Box).\textsuperscript{50}

The ICD is also used to prevent SCD in other patients at high risk, such as those with cardiac ion-channel abnormalities or structural heart diseases creating an arrhythmogenic substrate. Although prospective randomized trials in these relatively rare conditions are not likely to be pursued,\textsuperscript{51} case series show efficacy of the ICD in patients with long-QT syndromes,\textsuperscript{32} Brugada syndrome,\textsuperscript{53} hypertrophic cardiomyopathy,\textsuperscript{54,55} and arrhythmogenic right ventricular dysplasia.\textsuperscript{56} Current guidelines support its use in selected patients with these disorders.\textsuperscript{46}

An evaluation of the cost-effectiveness of the ICD using a Markov model\textsuperscript{57} revealed that prophylactic ICD implantation was both more effective and more expensive than control therapy. Consistent with the lower numbers needed to treat, the populations showing greatest cost-effectiveness of the ICD were those in MADIT I and MUSTT, with approximately $25,000 per life-year added. The ICD was less cost-effective in the MADIT II and SCD-HeFT populations, with $40,000 to $50,000 per life-year added, respectively. (Other data from SCD-HeFT showed a cost-effectiveness of $33,000.\textsuperscript{37}) Costs per quality-adjusted life-year ranged from $34,000 to $70,000. Not surprisingly, lowering the cost of the device or increasing longevity would improve cost-effectiveness.\textsuperscript{37} These costs are well within the range considered acceptable to society.\textsuperscript{58}

### Expanding Technologies

Implantable cardioverter-defibrillators were first developed by Dr Michel Mirowski, whose invention was prompted by the sudden death of a colleague. Ironically, at the time of its development, Mirowski emphasized that the ICD was “not a definitive treatment for recurrent malignant arrhythmia.”

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**Box. Centers for Medicare & Medicaid Services (CMS) Coverage Requirements for Implantable Cardiov"
mia and should not be regarded as a substitute for antiarrhythmic medications or other modes of therapy. The 3 main functions of the ICD are detection of arrhythmia; delivery of appropriate electrical therapy; and storage of diagnostic information, including electrograms and details of treated episodes. In addition, ICDs provide anti-bradycardia pacing, either single- or dual-chamber. The device consists of 2 components, the pulse generator and the lead electrode system. Current ICDs are only slightly larger than a pacemaker (25-45 cm³) and are similarly implanted in a subcutaneous pectoral pocket. Leads are inserted transvenously through the subclavian, axillary, or cephalic vein into the right ventricular apex (and the right atrial appendage for dual-chamber pacing).

The modern ICD combines high-energy defibrillation with 2 other electrical therapies, low-energy cardioversion and antitachycardia pacing, to terminate ventricular arrhythmias. Antitachycardia pacing terminates ventricular tachycardia without delivering a painful shock by pacing at a rate faster than the intrinsic tachycardia, entraining and interrupting the re-entrant circuit. Tiered therapy allows programming of these electrical options to treat tachycardias with rates within defined zones of detection. For example, a slower arrhythmia might be treated by antitachycardia pacing followed by low-energy shock and then high-energy shock, if needed. Ventricular fibrillation falls in a faster zone, prompting high-energy defibrillation. While antitachycardia pacing was initially used only to treat slower, stable ventricular tachycardia, the recent Pacing Reduces Shocks for Fast VT II (PAINFREE Rx II) trial found that empirically programmed antitachycardia pacing delivered during device charging (a function available in some devices) could treat faster ventricular tachycardias, reducing shocks by 70% with no adverse outcomes.

Dual-Chamber ICDs. While early ICDs could pace the ventricle, the deleterious effects of single-chamber pacing (ie, pacemaker syndrome, development of atrial tachyarrhythmias), together with the problems in detection and treatment of ventricular arrhythmias caused by implanting 2 devices, led to the incorporation of dual-chamber pacing capabilities. Dual-chamber ICDs offer the hemodynamic benefits of dual-chamber pacing in patients with bradycardias, with recent devices incorporating algorithms that provide atrial-based pacing while minimizing right ventricular pacing.

In most, although not all, studies, the dual-chamber device offers improved discrimination between ventricular and supraventricular arrhythmias, decreasing inappropriate shocks due to rapid supraventricular rhythms or physiologic sinus tachycardia. This is achieved using specific algorithms, such as those that analyze the relative timing of atrial and ventricular electrograms, or by inhibition of ICD discharge when the sensed atrial rate is faster than the ventricular rate, as is the case in atrial fibrillation. Further, for patients receiving ICDs, universal dual-chamber device implantation may be the least-expensive strategy.

Cardiac Resynchronization Therapy. Abnormal chamber mechanics—that is, intraventricular conduction delays resulting in dysynchronous contraction—contribute significantly to CHF. Left bundle-branch block, whether intrinsic or due to right ventricular pacing, impairs effective contraction by causing septal contraction before activation of the lateral wall of the left ventricle, creating dyssynchrony. This abnormality causes a reduced cardiac output due to shortened diastolic filling time, a result of the lengthening of isovolumetric contraction and relaxation times. In addition, delayed activation of the left ventricular lateral wall may lead to a contraction after aortic valve closure, reducing ventricular filling during diastole. These factors represent the likely mechanism for the increased mortality with dual-chamber pacing seen in the DAVID trial, as well as the increased CHF seen in patients receiving the ICD in MADIT II.

Cardiac resynchronization therapy, also known as biventricular pacing, can improve CHF in patients with left bundle-branch block through placement of a third lead through the coronary sinus into a venous branch along the free wall of the left ventricle (or epicardially). Pacing the left ventricle promotes earlier contraction, restoring physiologic synchrony of the ventricles. CRT improves not only cardiac output and ejection fraction, but symptoms as well, including improvements in NYHA class, 6-minute walking distance, and quality of life, along with lower hospitalization rates.

Further, CRT improves survival. The recent randomized Cardiac Resynchronization–Heart Failure (CARE-HF) trial evaluated the effects of CRT alone (pacing only) on morbidity and mortality in patients with NYHA class III or IV heart failure due to left ventricular systolic dysfunction and cardiac dyssynchrony. CRT significantly decreased mortality, with 82 deaths compared with 120 in the group receiving medical therapy (P < .002), as well as improved quality of life. However, 32% of the deaths in the CRT group were sudden, suggesting that a combination of CRT and defibrillation capabilities might improve survival.

The recently published Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial randomly assigned patients with CHF (NYHA class III or IV with LVEF <33%) and conduction delays (QRS intervals >120 ms) to receive conventional therapy alone, CRT alone, or CRT incorporated in an ICD. While patients in the CRT-alone group had a 19% risk reduction in the primary end point of death or hospitalization (P = .01), patients in the CRT plus ICD group had a significant improvement in total mortality, a relative reduction of 36%. A limitation of COMPANION was its lack of power to directly compare CRT with defibrillation vs CRT without defibrillation.
Further, in COMPANION, device benefit began immediately, while in CARE-HF; no treatment benefit was seen until 1 year, likely because the reverse remodeling with CRT is not immediate.

While the issue of CRT alone vs CRT plus ICD remains controversial, these data, in combination with those from SCD-HeFT, showing minimal benefit of a single-lead device in NYHA class III CHF, suggests that the combination of CRT plus ICD may provide the most benefit for patients with severe CHF. In response to this growing body of evidence, the recently revised ACC/AHA CHF Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult\(^9^0\) state that “there is strong evidence to support the use of CRT to improve symptoms, exercise capacity, quality of life, LVEF; and survival and to decrease hospitalizations in patients with persistently symptomatic heart failure undergoing optimal medical therapy who have cardiac dyssynchrony.” In addition to QRS duration, methods such as tissue Doppler imaging may further delineate patients with dysynchrony most likely to benefit from CRT.\(^6,7\) Three early case reports describe ventricular tachycardia resulting from CRT,\(^8^5-9^2\) attributed to epicardial left ventricular pacing. However, a recent analysis of 2 of the large CRT trials (totaling 880 CRT-treated patients) showed no increase in arrhythmia frequency with CRT.\(^9^0\)

The ongoing Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy trial (MADIT-CRT) will determine whether, in patients receiving a prophylactic ICD who have a widened QRS interval but less than NYHA class III heart failure, CRT in combination with the ICD will slow the progression of CHF to class III or IV.\(^9^7\)

### Table 4. Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>No.</th>
<th>Population</th>
<th>Mean Follow-up, mo</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSCIC,(^8^7)</td>
<td>Conventional therapy vs CRT</td>
<td>67</td>
<td>NYHA class III; QRS interval &gt;150 ms; LVEF &lt;35%; sinus rhythm</td>
<td>3</td>
<td>CRT resulted in improvement in 6-min walking distance (P &lt; .001).</td>
</tr>
<tr>
<td>MIRACLE,(^8^9)</td>
<td>Conventional therapy vs CRT</td>
<td>453</td>
<td>NYHA class III; QRS interval &gt;130 ms; LVEF ≤35%; LVEDD ≤55 mm; 6-min walking distance ≤450 m</td>
<td>6</td>
<td>CRT/ICD resulted in improved quality-of-life scores (P = .001), improved NYHA class (P &lt; .001), and 6-min walking distance (P = .006).</td>
</tr>
<tr>
<td>PATH-CHEF,(^7^7)</td>
<td>Crossover: biventricular vs optimal univentricular stimulation followed by opposite treatment</td>
<td>42</td>
<td>NYHA class III; QRS interval &gt;120 ms</td>
<td>12</td>
<td>No significant difference in peak oxygen or 6-min walking distance between biventricular and optimized univentricular pacing (left ventricular in 36 patients).</td>
</tr>
<tr>
<td>CONTAK-CD,(^8^8)</td>
<td>Conventional therapy vs CRT/ICD</td>
<td>490</td>
<td>NYHA class II/III; QRS interval &gt;120 ms; LVEF ≤35%</td>
<td>6</td>
<td>CRT/ICD improved peak oxygen consumption (P = .03) and 6-min walking distance (P = .04). Changes in NYHA class (P = .10) and quality-of-life scores (P = .40) were not statistically significant.</td>
</tr>
<tr>
<td>MIRACLE-ICD,(^8^9)</td>
<td>ICD vs CRT/ICD</td>
<td>369</td>
<td>NYHA class II/III; QRS interval &gt;120 ms; LVEF ≤35%</td>
<td>6</td>
<td>CRT/ICD improved quality-of-life scores (P = .02), NYHA class (P = .007), peak oxygen consumption (P = .04), and exercise function on a treadmill (P &lt; .001).</td>
</tr>
<tr>
<td>PATH-CHEF II,(^8^0)</td>
<td>Conventional therapy vs CRT/ICD, stratified by QRS interval into long-QRS (&gt;150 ms) and short-QRS (120 to 150 ms) groups</td>
<td>101</td>
<td>NYHA class II/III; QRS interval &gt;120 ms; LVEF ≤35%</td>
<td>3</td>
<td>Long-QRS group improved peak oxygen consumption (P &lt; .001), 6-min walking distance (P = .02), and quality-of-life scores (P = .004). Short-QRS group did not improve in any end point with active pacing.</td>
</tr>
<tr>
<td>COMPANION,(^7^9)</td>
<td>Conventional therapy vs CRT/ICD</td>
<td>1520</td>
<td>NYHA class III/IV; LVEF &lt;35%; QRS interval ≥120 ms; hospitalization for CHF within 12 mo</td>
<td>17</td>
<td>Reduction in total mortality with CRT alone (P = .06). Reduction in mortality with CRT/ICD (P = .003). HR, 0.64; 95% CI, 0.48-0.86. NNT = 11 over median 15-16 mo.</td>
</tr>
<tr>
<td>CARE-HF,(^9^2)</td>
<td>Conventional therapy vs CRT</td>
<td>813</td>
<td>NYHA class III/IV; LVEF &lt;35%; QRS interval ≥120 ms; LVEDD &lt;80 mm; additional criteria for dyssynchrony</td>
<td>29</td>
<td>Reduction in all-cause mortality with CRT vs conventional therapy (P &lt; .0002). CRT reduced the interventricular mechanical delay, end-systolic volume index, and area of the mitral regurgitant jet; increased LVEF; and improved symptoms and quality-of-life scores (P &lt; .01). HR, 0.64; 95% CI, 0.48-0.85. NNT = 12 at 2 y.</td>
</tr>
</tbody>
</table>

Abbreviations: CARE-HF, Cardiac Resynchronization—Heart Failure; CHF, congestive heart failure; CI, confidence interval; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT, cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSCIC, Multisite Stimulation in Cardiomyopathy; NNT, number needed to treat; NYHA, New York Heart Association; PATH-CHEF, Pacing Therapies for Congestive Heart Failure.

\(^*\)CRT/ICD indicates CRT incorporated into an ICD.

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**Atrial Defibrillators**

Because pharmacological treatment for atrial fibrillation is frequently ineffective \(^{98-100}\) and carries potentially life-threatening proarrhythmic effects, \(^{101-104}\) attention has focused on non-pharmacological therapies, including the atrial ICD, which recognizes and delivers a shock for atrial fibrillation. The overall efficacy in terminating atrial fibrillation is 70% to 90%, with no ventricular proarrhythmia \(^ {105}\) and good discrimination between atrial and ventricular tachyarrhythmias. \(^ {106}\) Rapid atrial pacing can terminate atrial tachycardias (often the precursor to atrial fibrillation) painlessly, \(^ {107}\) but efficacy is low. \(^ {108}\) Because atrial shocks are painful, devices programmed to be triggered by the patient may therefore be underused. \(^ {109}\) Only a very small percentage of all ICDs implanted (2%) are atrial defibrillators (2003 industry data courtesy of Medtronic; C. Gennaro, BSME, MBA, written communication, March 2004).

**Device Malfunction**

With expanding device technology has come an increase in malfunctions resulting in advisories and recalls, and with increasing indications for the ICD, the number of patients affected by advisories also will increase. \(^ {110,111}\) Death due to device malfunction is rare \(^ {110,111}\) but emotionally devastating when it occurs, as recently illustrated by the death of a college student with hypertrophic cardiomyopathy whose ICD failed to deliver therapy due to a short-circuiting device. \(^ {112,113}\) Since February 2005, there have been advisories involving all 3 leading device manufacturers (Guidant, Medtronic, and St Jude). \(^ {112}\) Patients and physicians faced with an advisory must weigh the risks of malfunction, which vary with the nature of the specific advisory and the patient’s underlying arrhythmia, with the risks of replacement. The Heart Rhythm Society convened a conference in September 2005 that brought together patients, physicians, industry representatives, and the US Food and Drug Administration to address device performance issues \(^ {113}\) and is currently working on guidelines to improve surveillance, analysis, and communication of device performance.

**CONCLUSIONS**

In summary, ICDs improve survival in an expanding population of patients. In addition to providing secondary prophylaxis in survivors of life-threatening ventricular arrhythmia, ICD implantation is now first-line therapy for primary prophylaxis in most patients with marked left ventricular dysfunction, regardless of etiology. Recent technological advances include resynchronization therapy and the incorporation of atrial defibrillation in some devices. Ongoing research and refined methodologies of risk stratification may continue to delineate groups with survival benefit from ICDs.

**Author Contributions:** Drs Goldberger and Lampert had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** analysis and interpretation of data; critical revision of the manuscript for important intellectual content: Goldberger, Lampert. Acquisition of data; drafting of the manuscript: statistical analysis: Goldberger.

**Study supervision:** Lampert.

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**REFERENCES**


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RECEIVED BIVENTRICULAR PACING TREATMENT.

PETTER MYOCARDIAL IMAGING IN PATIENTS WITH HEART FAILURE SECONDARY TO IDIOPATHIC DILATED OR TO ISCHEMIC MYOCARDIAL DISEASE.

PRINCIPLES AND CURRENT CLINICAL STATUS OF CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE AND INTRAVENTRICULAR CONDUCTION DELAY.


