

# The Role of the Implantable Cardioverter-Defibrillator for Prevention of Sudden Cardiac Death

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Sudden cardiac death, which accounts for approximately 350 000 deaths each year, is a major health care problem. Antiarrhythmic drugs have not been reliable in preventing sudden cardiac death. Although  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, and revascularization play a role in prevention of sudden cardiac death, the development and subsequent refinement of the implantable cardioverter-defibrillator has made the most important contribution to its management. Several randomized, controlled trials have demonstrated improved survival in patients resuscitated from cardiac arrest. Two recent trials also suggest a role for

primary prevention in selected patients with coronary artery disease, ventricular dysfunction, and nonsustained ventricular tachycardia in whom sustained ventricular tachycardia is induced. Further technological refinements and development of new, more sensitive risk stratifiers with a higher positive predictive value for sudden cardiac death will expand the indications for this life-saving therapy.

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Sudden cardiac death affects approximately 350 000 people per year in the United States, and at least 1 million people per year develop conditions that place them at risk for sudden cardiac death in the future. Survivors of one sudden cardiac death episode have a recurrence rate of 35% to 50% in 2 years, which 85% of the time is the result of ventricular tachycardia or ventricular fibrillation. Although coronary revascularization,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, some antiarrhythmic agents, and antiarrhythmic surgery can reduce the chance for sudden cardiac death, development of the implantable cardioverter-defibrillator (ICD) has had the greatest impact on specifically preventing sudden death.

The ICD was the result of work by Michel Mirowski, who implanted the first defibrillator in a human in 1980 (1). The initial automatic implantable defibrillators were large, required a thoracotomy to place epicardial defibrillating patches, and were nonprogrammable. Shortly thereafter, synchronization to the QRS of ventricular tachycardia led to a change in name to "automatic implantable cardioverter-defibrillator." With the development of devices by other companies, the generic term, ICD, has become most appropriate for these devices as a group.

In 1985, the U.S. Food and Drug Administration approved the ICD, and in the past 15 years this device has evolved rapidly and gained widespread acceptance. The ICD has been substantially reduced in size; can be implanted transvenously as a pacemaker would be; and can be programmed for sensing, antitachycardia pacing, and defibrillating. The rapidity with which these changes have occurred testifies to the effectiveness of the device in convert-

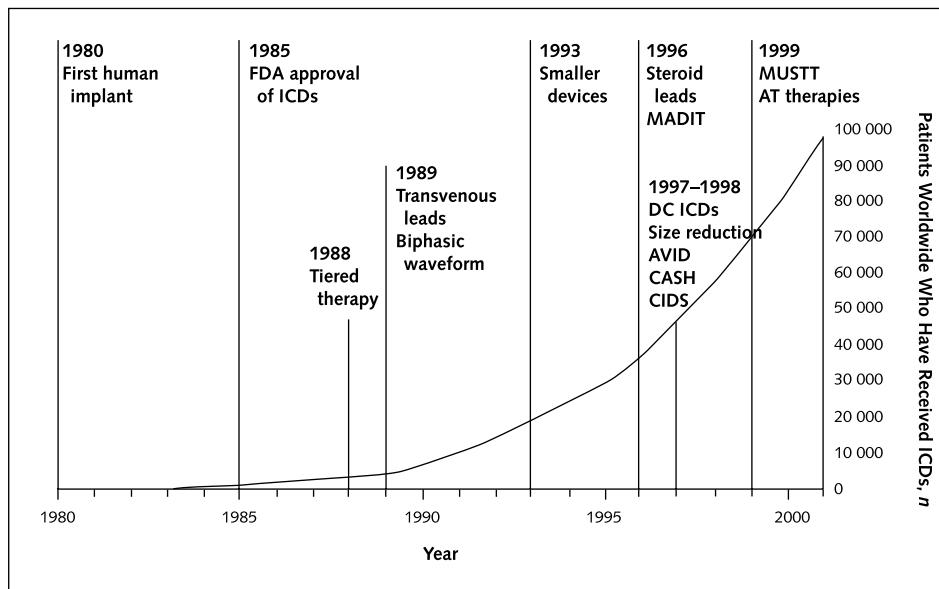
ing fatal ventricular arrhythmias to sinus rhythm. Currently, ICDs may be single-chambered or dual-chambered, have sophisticated algorithms for detection of supraventricular and ventricular arrhythmias, and can be programmed to deliver multiple therapeutic options, all in a device approximately 40 mL in size.

The historic evolution of the ICD is shown in **Figure 1**. The impact of these evolutionary changes on hospital costs and lengths of stay is shown in **Figure 2**. The risks associated with implantation of transvenous ICDs are comparable to those incurred with implantation of standard pacemakers; the only added risk is that associated with testing of the device. In our experience, implantation-related mortality is less than 0.5%. We discuss the current indications for ICD use in primary and secondary prevention of sudden cardiac death.

## ICD THERAPY FOR PREVENTION OF SUDDEN CARDIAC DEATH IN PATIENTS WITH DOCUMENTED OR SUSPECTED VENTRICULAR TACHYARRHYTHMIAS

This section discusses three types of patients: 1) those who have survived cardiac arrest or who have documented hemodynamically intolerated ventricular tachycardia (that is, with such symptoms as syncope, angina, or heart failure), 2) those with sustained ventricular tachycardia that is hemodynamically tolerated, and 3) those with syncope without documented arrhythmias but in whom ventricular tachyarrhythmias are considered the most likely cause.

Figure 1. Evolution of implantable cardioverter-defibrillator (ICD) therapy.



With the introduction of smaller, multiprogrammable, transvenously implanted ICDs, acceptance and use of these devices have increased markedly. Values for 2000 are estimates. AT = antitachycardia pacing; AVID = Antiarrhythmic Versus Implantable Defibrillator Trial; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; DC = dual chamber; FDA = U.S. Food and Drug Administration; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MUSTT = Multicenter Unsustained Tachycardia Trial.

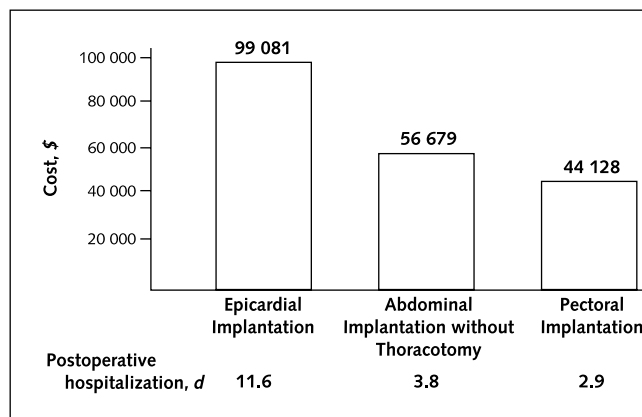
### Patients with Aborted Cardiac Arrest or Hemodynamically Untolerated, Uniform Ventricular Tachycardia

The potential benefit of ICD therapy for secondary prevention in patients with hemodynamically intolerated ventricular arrhythmias has been suggested for many years on the basis of observational and nonrandomized studies (2–5). Confidence in conventional antiarrhythmic therapy (that is, therapy other than amiodarone) to prevent sudden

death has been eroded by such studies as the Cardiac Arrest Study in Seattle: Conventional Versus Amiodarone Drug Evaluation and, to a lesser extent, the Electrophysiologic Study Versus Electromagnetic Monitoring trial, as well as by an increased appreciation for the proarrhythmic side effects of antiarrhythmic therapy (6–9). Nonetheless, many doubted the ability of ICD therapy to provide a significant total mortality benefit, mostly because of the “competing causes of death” (10) in patients with ventricular arrhythmias and significant structural heart disease (of which refractory congestive heart failure is the most important). This was the setting for the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (11), which provided the first randomized, controlled comparison of ICD therapy with “best” antiarrhythmic therapy—essentially, empirical amiodarone therapy—in patients with aborted cardiac arrest or poorly tolerated ventricular tachycardia. The trial, which included 1016 patients randomly assigned to ICD or drug therapy, was terminated prematurely after interim analysis demonstrated that ICD therapy reduced total mortality by 27% at 2 years (25% vs. 18%; absolute risk reduction, 7 percentage points;  $P < 0.02$ ) (11).

The significance of this result was questioned on several fronts. First, the 27% reduction in mortality resulted

Figure 2. Reduction in costs of implantation with the evolution of implantable cardioverter-defibrillators.



in a mean duration of life saved of only 2.7 months at 3 years. However, the survival benefit in AVID may have been undermined by early termination of the trial, as well as by 18.9% crossover from amiodarone to ICD therapy. Second, many expressed concern that AVID was not representative of the larger population of patients with life-threatening ventricular arrhythmias. This criticism was somewhat muted by similar findings of the Canadian Implantable Defibrillator Study (CIDS) (12) and the Cardiac Arrest Study Hamburg (CASH) (13), in which ICD therapy provided a reduction in total mortality of 19.6% and 37% at 2 years, respectively (Table 1). However, the absolute risk reduction was 5 percentage points over 3 years in CIDS and 7.5 percentage points over 2 years in CASH, and the results of CIDS were not statistically significant ( $P = 0.07$ ). Moreover, CASH demonstrated a benefit of ICD therapy only when the amiodarone and  $\beta$ -blocker groups were combined on a post hoc basis. These limitations may have resulted from lack of sufficient statistical power in both studies. In addition, both CIDS and CASH took 7 years to recruit patients, leading to concern over whether the population studied was representative of the population at risk. Finally, some wondered whether the apparent benefit was due instead to the nonequivalent use

of  $\beta$ -blockers in the ICD group (42%) relative to the amiodarone (17%) treatment group, even though ICD therapy demonstrated persistent benefit after post hoc adjustment for this variable. Increased use of  $\beta$ -blockers in the ICD group also occurred in CIDS. It could also be argued that more patients in both groups may have benefited from  $\beta$ -blockers (14–17), coronary revascularization (particularly in light of the Coronary Artery Bypass Grafting Patch Trial findings) (18), and angiotensin-converting enzyme inhibitors. Nonetheless, the AVID trial, CIDS, and CASH were consistent in their demonstration of the superiority of ICD therapy over antiarrhythmic drug therapy in patients with life-threatening ventricular arrhythmias.

Despite the power of these results, some have argued against uniform prescription of ICD therapy for all patients with poorly tolerated ventricular arrhythmias. Subgroup analysis of the AVID trial suggested that ICD therapy conferred no advantage over treatment with amiodarone in patients with relatively preserved left ventricular function (ejection fraction  $> 0.35$ ) (19). We disagree with this idea. These patients, who have relatively little risk for cardiac death aside from arrhythmic death, should benefit from ICD therapy in the long term. Trial design factors, such as low event rates, short observation periods, and early trial

**Table 1. Trials Comparing Implantable Cardioverter-Defibrillators with Antiarrhythmic Drug Therapy in Patients with Ventricular Tachycardia or Ventricular Fibrillation\***

| Study Characteristic                       | AVID (1993–1997)   | CIDS (1990–1998)  | CASH (1987–1998)   |
|--|--|---|--|
| Protocol                                   | ICD vs. empirical therapy with amiodarone or sotalol†      | ICD vs. empirical amiodarone therapy  | ICD vs. empirical therapy with amiodarone, metoprolol, or propafenone‡ |
| Sample size, <i>n</i>                      | ICD: 507<br>Amiodarone or sotalol: 509                     | ICD: 328<br>Amiodarone: 331   | ICD: 99<br>Amiodarone: 92<br>Metoprolol: 97<br>Propafenone: 56         |
| Inclusion criteria                         | Survivor of VT, VT with syncope, or VT with EF $\leq 0.40$ | Survivor of VT, VT with syncope, or VT with EF $\leq 0.35$ and cycle length $\leq 400$ ms | Survivor of VT (no EF requirement)                                     |
| Mortality, %                               |  |   |  |
| 1 year                                     | ICD: 11<br>Drug: 18  | –   | –  |
| 2 years                                    | ICD: 18<br>Drug: 25  | –   | ICD: 12.1<br>Drug: 19.6  |
| 3 years                                    | ICD: 25<br>Drug: 36  | ICD: 25<br>Drug: 30   | –  |
| Reduction in mortality with ICD therapy, % |  |   |  |
| 1 year                                     | 39   | –   | –  |
| 2 years                                    | 27   | –   | 37   |
| 3 years                                    | 31   | 20  | –  |

\* AVID = Antiarrhythmics Versus Implantable Defibrillators; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.

† Most patients in the drug therapy group received amiodarone.

‡ After interim analysis in March 1992, enrollment in the propafenone group was discontinued because mortality among these patients was significantly increased compared with patients who received ICDs.

**Table 2. Authors' Indications for Implantable Cardioverter-Defibrillator Therapy\***

|  |
|--|
| <p>Class I: Conditions for which there is convincing evidence that ICD therapy is effective</p> <ul style="list-style-type: none"> <li>Cardiac arrest due to ventricular fibrillation or ventricular tachycardia not due to a transient or reversible cause</li> <li>Spontaneous, sustained ventricular tachycardia</li> <li>Syncope of undetermined origin with inducible ventricular tachycardia or ventricular fibrillation on electrophysiologic study</li> <li>Nonsustained ventricular tachycardia with previous myocardial infarction, ejection fraction &lt; 0.35, and inducible ventricular tachycardia or ventricular fibrillation on electrophysiologic study</li> </ul>  |
| <p>Class II: Conditions for which evidence of ICD efficacy is limited</p> <ul style="list-style-type: none"> <li>Patients with cardiac arrest in whom electrophysiologic testing is precluded by other medical conditions</li> <li>Patients who have nonischemic cardiomyopathy with syncope presumed to be due to ventricular tachyarrhythmias but no inducible arrhythmia on electrophysiologic testing</li> <li>Familial or inherited conditions with a high risk for life-threatening ventricular tachycardia or ventricular fibrillation (such as the Brugada syndrome, the long QT syndrome, or hypertrophic cardiomyopathy)</li> <li>Cardiac arrest due to transient or reversible causes that are not preventable</li> </ul> |
| <p>Class III: Conditions for which there is evidence that ICD therapy is not indicated</p> <ul style="list-style-type: none"> <li>Incessant ventricular tachycardia or ventricular fibrillation</li> <li>Ventricular fibrillation or ventricular tachycardia resulting from arrhythmias amenable to surgical or catheter ablation</li> <li>Significant psychiatric illness</li> <li>Terminal illness with projected life expectancy of 6 months</li> <li>New York Heart Association class IV drug-refractory congestive heart failure in patients who are not candidates for cardiac transplantation</li> </ul>  |

\* Adapted from reference 26. ICD = implantable cardioverter-defibrillator.

termination, make this benefit difficult to prove statistically. Patients with very poor left ventricular function (ejection fraction < 0.20) may not benefit from ICD therapy, particularly in the long run, because they have a high rate of death from comorbid conditions. Thus, patient selection and trial design markedly influence statistical results. Application of the data from these trials to individual patients needs to be done with caution because of the inherent limitations of randomized, controlled trials.

### Patients with Syncope Suspected To Result from Ventricular Tachyarrhythmias and Inducible Ventricular Arrhythmias with Programmed Ventricular Stimulation

It is well known that patients with unexplained syncope and left ventricular dysfunction have rates of mortality and event-free survival similar to those in patients resuscitated from a cardiac arrest (11). This was confirmed in the small subgroup of patients with syncope and inducible ventricular tachycardia in the AVID trial (11). In the observational AVID registry (20), patients with unexplained

syncope (mortality, 12.3% at 16.9 months) or syncopal ventricular tachycardia (mortality, 21.2%), had as poor a prognosis as patients resuscitated from cardiac arrest (mortality, 17.0%). This finding led investigators to suspect that similar mechanisms were at work in these two patient populations. To date, no randomized trial has evaluated the most appropriate therapy for such patients—ICDs. However, these data suggest that the benefit of ICD therapy in patients with syncope should equal that observed in the “higher-risk” patient cohorts discussed in the preceding section.

In a retrospective analysis of our own data, the frequency of appropriate ICD therapy during follow-up in patients who had an ICD implanted for unexplained syncope believed to be due to ventricular tachyarrhythmias was similar to that among survivors of cardiac arrest (21). Link and coworkers (22) reported that patients with syncope and inducible ventricular tachycardia have a high likelihood of appropriate ICD therapy during follow-up, with an actuarial probability of 22% at 1 year and 50% at 3 years. Appropriate ICD therapy was determined by analysis of stored electrocardiograms and counters to verify that the rhythm being treated was ventricular tachycardia or ventricular fibrillation.

In a recent case–control study, Knight and colleagues (23) examined the incidence of appropriate ICD shocks in patients with dilated cardiomyopathy and a history of syncope. Patients had negative preimplantation electrophysiologic studies, but ICD therapy was nonetheless prescribed because of the low sensitivity of programmed stimulation in this cohort (24). Although the sample was small, 50% of patients had appropriate ICD therapy during a mean follow-up of 24 months. These data demonstrate the ominous prognostic implications of syncope in the setting of advanced heart disease and suggest potential benefit of ICD therapy. As cautioned by Josephson (25) in an accompanying editorial, syncope due to other causes must be excluded before ICD implantation is considered. Of note, although the presence of unexplained syncope and inducible ventricular tachycardia is considered an indication for ICD implantation in the recent recommendations of an American College of Cardiology/American Heart Association task force (26), unexplained syncope in the absence of inducible ventricular tachycardia is not (Table 2). Reconsideration of patients with the latter condition is in order, in light of Knight and colleagues' preliminary findings (23).

### Patients with Hemodynamically Tolerated Ventricular Tachycardia

The incidence of sudden cardiac death in patients who initially present with hemodynamically tolerated ventricular tachycardia is unknown, largely because of confounding effects of noncontrolled antiarrhythmic drug therapy. Nonetheless, the annual mortality rate from sudden cardiac death in this population is estimated to be 2% to 5% (27, 28). Other observations suggest that the incidence of sudden cardiac death in this setting may be even higher, leading some investigators to believe that ICD therapy may be helpful in this setting; however, no data to date from randomized, controlled trials support this hypothesis.

In a retrospective analysis of the Electrophysiologic Study Versus Electromagnetic Monitoring study, Caruso and associates (29) reported a 20% incidence of arrhythmic death at 2 years in patients who initially presented with hemodynamically tolerated ventricular tachycardia. However, the vague definition of “arrhythmic death” and the potential role of drug-induced proarrhythmia make this finding difficult to interpret. Bocker and coworkers (30) observed rapid, presumably fatal ventricular tachycardia (cycle length < 250 ms) requiring ICD therapy in 11 of 50 patients who presented with tolerated ventricular tachycardia (many of whom were receiving drug therapy) over a mean ( $\pm$ SD) follow-up of  $17 \pm 12$  months. In both of these studies, electrophysiologic study did not predict which patients would have more rapid ventricular tachycardia in follow-up. This may be related in part to the patient population evaluated. Patients with cardiomyopathy and hemodynamically tolerated ventricular tachycardia have been shown to have a high incidence of sudden death despite apparently effective antiarrhythmic therapy (24), and their overrepresentation in these studies may have contributed to the outcomes. Other limitations of these analyses, particularly related to changes in antiarrhythmic drug therapy that were not controlled for during follow-up and the potential role of proarrhythmia, further undermine confidence in pharmacologic therapy, even for tolerated ventricular tachycardia.

There has been some enthusiasm for primary catheter ablation therapy in patients with hemodynamically tolerated ventricular tachycardia associated with coronary artery disease (31). The incidence of rapid ventricular tachycardia, ventricular fibrillation, and mortality related to sudden cardiac death after successful catheter ablation for tolerated ventricular tachycardia is controversial and ranges from 1%

to 10% (31, 32). In our experience, patients with no structural heart disease and those with single-vessel coronary artery disease have a risk for sudden cardiac death of less than 1% over 2 years. In a recent study by El Shalakany and colleagues (33), no sudden deaths followed successful ablation of tolerated, clinical ventricular tachycardias, despite lack of therapy for other inducible (slow and fast) forms of ventricular tachycardias. Of note, in that study, all patients with tolerated ventricular tachycardia continued therapy with antiarrhythmic drugs that were taken at the time of presentation. Patients with ventricular tachycardia due to cardiomyopathy should not be considered comparable to those with previous infarction.

Given the persistent arrhythmia substrate after catheter ablation procedures, there is no reason to believe that the incidence of sudden cardiac death should differ from that in the index population not treated with ablation. A recent cost analysis of ablation therapy in our laboratories, assuming a 75% success rate and 25% recurrence rate, found ablation to be the most cost-effective approach as long as the rate of sudden death was 2% to 4%. However, the limited number of skilled operators and other factors that will reduce the success rate on an intention-to-treat basis make widespread use of ablative therapy unreasonable. Because of these limitations and the reduction in ICD shocks made possible by the efficacy of antitachycardia pacing, ICD implantation is increasingly the therapy of choice for this indication as well.

### ICD THERAPY FOR PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

Primary prevention of sudden cardiac death—that is, prevention of the initial episode of cardiac arrest or sudden cardiac death—requires identification of persons at risk for these events. Since the entire population is at risk for sudden cardiac death, screening tools must be developed to identify the persons most likely to benefit from costly, potentially risky interventions. Several invasive and noninvasive tests have been used, alone and in combination, to stratify patients at risk for sudden cardiac death. These include New York Heart Association (NYHA) classification, ejection fraction, heart rate variability, signal-averaged electrocardiography, baroreceptor responsiveness, T-wave alternans, nonsustained ventricular tachycardia, and electrophysiologic testing. To date, randomized trials of ICDs for primary prevention of sudden cardiac death have

**Table 3. Trials Comparing Implantable Cardioverter-Defibrillators with Conventional Therapy for Primary Prevention of Sudden Cardiac Death\***

| Study Characteristic                    | MADIT (1990–1996)   | MUSTT (1993–1999)†   |
|---|---|--|
| Protocol                                | ICD vs. conventional therapy (mainly amiodarone)  | Electrophysiologically guided therapy (ICD or drug therapy) vs. no electrophysiologically guided therapy |
| Sample size, <i>n</i>                   | ICD: 95<br>Conventional therapy: 101  | Guided ICD: 161<br>Guided drug therapy: 190<br>No guided therapy: 353                                    |
| Inclusion criteria                      | Previous Q-wave myocardial infarction, EF ≤ 0.35, asymptomatic nonsustained VT, and inducible VT not suppressible with procainamide therapy | Coronary artery disease, EF ≤ 0.40, asymptomatic nonsustained VT, and inducible VT                       |
| Reduction in mortality with ICD therapy | 54% at 27 months  | 74% at 60 months   |

\*EF = ejection fraction; ICD = implantable cardioverter-defibrillator; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MUSTT = Multicenter Unsustained Tachycardia Trial; VT = ventricular tachycardia.

† Preliminary results as of March 1999.

focused on one population: patients who have coronary artery disease with abnormal ventricular function. Three recent randomized trials evaluated the efficacy of ICD for prevention of sudden cardiac death, and others are under way. We review the three completed trials, all of which studied patients with coronary artery disease and impaired ventricular function.

**Trials in Patients with Low Ejection Fraction, Asymptomatic Nonsustained Ventricular Tachycardia, and Sustained Ventricular Tachycardia Induced during Electrophysiologic Studies**

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) (34) enrolled patients with previous Q-wave myocardial infarction, left ventricular ejection fraction of 0.35 or less, and nonsustained ventricular tachycardia but no previous cardiac arrest or hemodynamically intolerated ventricular tachycardia (syncope) (Table 3). The entry case of nonsustained ventricular tachycardia must have occurred at least 3 weeks after myocardial infarction. It is unclear whether or how many patients with a history of hemodynamically tolerated monomorphic ventricular tachycardia were included in the trial. Electrophysiologic studies were performed in the absence of antiarrhythmic drug therapy. Intravenous procainamide was then given to patients with inducible sustained ventricular tachycardia. Patients with persistently inducible sustained ventricular tachycardia in the presence of procainamide therapy were eligible for randomization to receive either an ICD or “conventional” antiarrhythmic therapy. The latter treatment was left to the discretion of individual investigators; however, 74% of patients assigned to the “conventional” therapy group received empirical amiodarone. The

study had no control group, and no information was given about how patients responded to procainamide.

A total of 196 patients were enrolled. After an average follow-up of 27 months, the trial was stopped because the investigators observed a 54% reduction in total mortality for the patients assigned to the ICD group. Actuarial mortality in the conventional treatment group was 32% at 2 years, and the absolute reduction in overall mortality associated with ICD therapy was 17 percentage points (from 32% to 15%) (Table 3).

Patients enrolled in MADIT had advanced coronary disease, with an average left ventricular ejection fraction of 0.26. Two thirds of patients had NYHA class II or III heart failure. The use of β-adrenergic blocking agents was low in both study groups (15% in the conventional therapy group and 28% in the ICD group). However, the benefit of ICD therapy in terms of overall mortality remained significant in multivariate analysis. Although the primary end point of the trial was total mortality, post hoc analyses suggested that the survival benefit of ICDs was due primarily to a reduction in sudden cardiac death. However, the ICD group also had fewer nonsudden deaths, raising the possibility that greater use of β-blocking agents in patients assigned to ICD therapy may have contributed to the observed benefits associated with ICD therapy.

The second trial supporting the use of ICDs for primary prevention of sudden cardiac death was the Multicenter Unsustained Tachycardia Trial (MUSTT) (35, 36) (Table 3). This trial was designed to assess the ability of antiarrhythmic therapy (ICDs or drugs) guided by electrophysiologic testing to reduce the risk for sudden cardiac death in patients with coronary artery disease, left ventric-

ular ejection fraction of 0.40 or less, inducible ventricular tachycardia, and asymptomatic nonsustained ventricular tachycardia occurring more than 96 hours after myocardial infarction or revascularization (percutaneous or surgical). No patient had a history of sustained ventricular tachycardia. Patients underwent baseline electrophysiologic study in the absence of antiarrhythmic drugs. Those who had sustained ventricular tachycardia induced were then randomly assigned to one of two groups: a control group that received neither ICD nor antiarrhythmic agents or a group treated with antiarrhythmic therapy (drugs or ICDs) guided by serial electrophysiologic testing. Antiarrhythmic drugs were tested first, and patients who did not respond to drugs (as judged by electrophysiologic testing) received an ICD. Antiarrhythmic drug therapy was considered successful if it rendered the ventricular tachycardia noninducible or was hemodynamically tolerated. Therapy with  $\beta$ -adrenergic blocking agents and angiotensin-converting enzyme inhibitors was recommended strongly for patients in both treatment groups.

In MUSTT, 704 of the 767 eligible patients (92%) were assigned to the treatment or control group. Patients in whom ventricular tachycardia was not inducible were followed in a registry. Over 5 years of follow-up, the risk for sudden cardiac death or cardiac arrest (the primary end point of the trial) in the control group was 32%; total mortality for this group was 48%. The patients who received electrophysiologically guided therapy experienced a 27% lower risk of arrhythmic death or cardiac arrest, and total mortality was reduced by 20%. The improved survival in the group that received electrophysiologically guided therapy was due entirely to use of ICDs. The absolute risk reduction for ICD therapy versus control was 24 percentage points (48% vs. 24%). Patients treated with pharmacologic antiarrhythmic therapy without ICDs had event rates very similar to those of the untreated controls. The risk for arrhythmic death or cardiac arrest over 5 years in patients treated with ICDs was reduced by 74% compared with patients treated with electrophysiologically guided pharmacologic antiarrhythmic therapy and those who received no antiarrhythmic therapy (32% vs. 9% [absolute risk reduction, 23 percentage points]).

The characteristics of patients enrolled in MUSTT were similar to those in MADIT. The average left ventricular ejection fraction was 0.30. Fewer patients in MUSTT had heart failure, and 76% were in NYHA functional class I or II. Use of  $\beta$ -blockers was greater in MUSTT than in

MADIT, with 35% of patients receiving these drugs; however, patients assigned to no ICD or antiarrhythmic drug therapy did not differ significantly from those assigned to electrophysiologically guided therapy.

The results of these two trials demonstrated the ability of the ICD to reduce mortality among patients at high risk for sudden cardiac death who never experienced cardiac arrest (Table 3). In addition, MUSTT also established the risk for arrhythmic death or cardiac arrest in patients with coronary disease, left ventricular dysfunction, or asymptomatic nonsustained ventricular tachycardia who have inducible sustained ventricular tachycardia. The control group in this trial, which received  $\beta$ -blockers and angiotensin-converting enzyme inhibitors alone, experienced a 5-year arrhythmic event rate of 32% (Kaplan–Meier analysis) and total mortality of 48%. Of note, in both trials ICDs were implanted only in patients who did not respond to antiarrhythmic drugs, as tested in the electrophysiology laboratory. Thus, neither trial proved efficacy in patients who respond to drugs at electrophysiologic testing. However, given the poor outcome of patients treated with electrophysiologically guided antiarrhythmic drug therapy in MUSTT, it does not seem reasonable to require failure of drug therapy before using ICDs in appropriate patients.

Of note, MUSTT was not designed to compare ICD and pharmacologic therapy. Only a small number of patients were given amiodarone (11% of the antiarrhythmic group). In these patients, amiodarone had to demonstrate an electrophysiologic beneficial response (that is, prevention of inducibility or slowing to hemodynamic tolerance) in order to be administered. The possibility that electrophysiologically guided amiodarone therapy might be beneficial in this group of patients has not been explored.

### Patients with Low Ejection Fraction and Positive Signal-Averaged Electrocardiography

The third recent randomized trial of primary prevention of sudden cardiac death showed no benefit of treatment with ICDs. The Coronary Artery Bypass Grafting Patch Trial (18) tested the hypothesis that ICDs would reduce total mortality in patients undergoing coronary artery bypass surgery who had left ventricular dysfunction (ejection fraction  $\leq$  0.35), abnormal signal-averaged electrocardiograms, and no history of symptomatic ventricular arrhythmias. The trial randomly assigned 900 patients to receive an ICD or no ICD at the time of coronary artery

bypass surgery. Over an average follow-up of 32 months, the actuarial total mortality rates in the control and ICD therapy groups were nearly identical: 24% and 27%, respectively ( $P > 0.2$ ).

Several characteristics of patients enrolled in the Coronary Artery Bypass Grafting Patch Trial were similar to those of patients in MUSTT and MADIT. The average ejection fraction was 0.27, and 73% of patients had NYHA functional class II or III heart failure. Use of  $\beta$ -blockers (including sotalol) was relatively low: 18% of patients assigned to ICD and 24% of those assigned to no ICD. The lack of benefit from ICD therapy suggests that ischemia contributes substantially to mortality and that correction of ischemia, even in some patients with very abnormal left ventricular systolic function, may reduce mortality. The Coronary Artery Surgery Study (37) showed that revascularization in patients with double- or triple-vessel disease was associated with a decrease in sudden cardiac death. However, mortality among patients enrolled in that study was high regardless of whether they were treated with ICDs, and sudden cardiac death accounted for a significant minority of events in both treatment groups. Another conclusion may be that the signal-averaged electrocardiography is not as sensitive a risk stratifier as electrophysiologic study.

There is another group of patients at high risk for sudden cardiac death in whom the benefit of prophylactic ICD implantation is unproven. Patients with congestive heart failure constitute an increasing proportion of hospital admissions. Fifty percent of deaths in patients with heart failure occur suddenly, and ventricular tachyarrhythmias are thought to be responsible for many of these events. However, patients with heart failure are also at risk for sudden death from noncardiac causes, such as pulmonary emboli. In addition, the occurrence of ventricular tachyarrhythmias in such patients may not always be due to a primary electrical process, but secondary to severe heart failure.

The extent to which ICDs can reduce mortality in this population is not clear. One trial currently enrolling patients seeks to determine the potential benefit of ICDs in this population. The Sudden Cardiac Death in Heart Failure Trial (38) was begun in 1997 to test the hypothesis that amiodarone or ICD will improve survival in patients with dilated cardiomyopathy (idiopathic or due to coronary disease), left ventricular ejection fraction of 0.35 or less, and NYHA class II or III symptoms. Patients are ran-

domly assigned in equal numbers to one of three treatment groups: amiodarone, placebo, or ICD. This study is currently enrolling patients, and results will not be available for several years. The MADIT II (39) will select high-risk patients who have had infarction with ejection fractions of 0.30 or less and randomly assign them to ICD therapy or conventional therapy (angiotensin-converting enzyme inhibitors and  $\beta$ -blockers). Several other trials in North America and Europe are planned to address the role of ICDs in primary prevention in patients who have had myocardial infarction and those with congestive heart failure by using different risk stratifiers, alone and in combination (for example, ejection fraction, heart rate variability, signal-averaged electrocardiogram, baroreceptor responsiveness, T-wave alternans, and nonsustained ventricular tachycardia).

Many other patients at high risk for sudden death have been recognized as appropriate candidates for ICDs. These indications are the result of observational data and expert opinion rather than controlled prospective trials. They are based in part on guidelines established by the joint American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation) (26). Indications include severely symptomatic sustained ventricular tachycardia in patients who are awaiting cardiac transplantation; familial conditions associated with high risk for sudden cardiac death, such as the long QT syndrome and hypertrophic cardiomyopathy; and family history of sudden cardiac death.

Finally, ICD therapy is not indicated in several types of patients at risk for sudden cardiac death. These include patients with ventricular tachyarrhythmias for which primary cures exist, such as those associated with the Wolff-Parkinson-White syndrome, and those curable by radiofrequency catheter ablation. Implantable cardioverter-defibrillators are also not indicated if the device would not improve survival or overall quality of life, such as in patients with class IV congestive heart failure who are not candidates for cardiac transplantation.

## CONCLUSIONS

Several well-designed clinical trials have demonstrated that ICDs can reduce the risk for arrhythmic death and overall mortality in selected patient populations. Rapid improvements in ICD technology have produced smaller, multiprogrammable devices with diagnostic and therapeutic

tic capabilities and greater longevity. It is likely that ICDs will be used increasingly for primary prevention of sudden cardiac death. Our challenge is to better define which patients are likely to derive the most benefit from this treatment. Newer risk stratifiers, such as T-wave alternans, heart rate variability, and QT dispersion, are being evaluated individually and together with more traditional risk stratifiers in the hope of better defining patient populations in whom ICD or other therapies can be successfully and cost-effectively applied.

Results of randomized trials should be applied with caution to individual patients. Trial design, which imposes inherent entry bias and finite study duration, limits the usefulness of results in indefinite treatment of patients. The cost-effectiveness of any therapy will be markedly influenced by its price; reduction of costs of ICDs will therefore enhance their cost-effectiveness. With these limitations in mind, our recommendations for ICD therapy are shown in Table 2.

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