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?)

Derek V. Exner, MD, MPH; George J. Klein, MD; Eric N. Prystowsky, MD

Sudden cardiac death (SCD) is a major public health problem in North America, responsible for approximately 400,000 deaths annually. Most episodes of SCD in ambulatory populations result from ventricular tachyarrhythmias, whereas bradyarrhythmias may be important in some populations, notably hospitalized patients with advanced heart failure. A prior article in this series by Zipes and Wellens provides a detailed review of the pathogenesis of SCD, its underlying causes, and treatment strategies.

ICD Therapy
The availability of a therapy that reliably terminates the vast majority of life-threatening tachyarrhythmic and bradyarrhythmic events has tremendous clinical appeal. The implantable cardioverter defibrillator (ICD) represents such a therapy. Despite its appeal, the ICD is imperfect. Currently, systems are costly, have a limited life expectancy, and are subject to complications in the long term. Furthermore, many patients at risk for SCD are at risk of dying from causes that the ICD would not alter. The impact of ICD shocks also merits consideration. Evidence links multiple shocks with myocardial injury and fibrosis, and sporadic shocks are associated with significant, independent reductions in quality of life. Compared with patients not having shocks, patients in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial who had ≥1 shocks in the initial year of follow-up had significant declines in self-perceived physical functioning and mental well-being, independent of ejection fraction (EF), social circumstances, and medication use. The reduction in quality of life associated with shocks was of a magnitude similar to clinically important adverse effects from amiodarone. Cost-efﬁcacy is a vital issue in settings of limited or restricted health care resources and is particularly relevant as ICD use is expanded to include patients sharing only some similarity to populations in which it has been demonstrated to be effective, so-called indication creep.

Identification of High-Risk Populations
The most important limitation in effecting a large reduction in SCD is a lack of accurate and reliable methods of identifying most individuals at risk. Although subsets of patients at high risk can be identified with current strategies, they represent a minority of those destined to have SCD (Figure 2). Because many cardiac arrests occur in persons with multiple coronary risk factors or ischemic symptoms for which they had not sought medical attention, appropriate attention to prophylactic therapy with antiplatelet drugs, statins, and other agents may significantly reduce the burden of SCD. Widespread use of automated external defibrillators may be another effective way of reducing SCD in the general population but requires confirmation.

Evolution of the ICD
Over the past 3 decades, tremendous progress has been made in the field of device therapy for preventing sudden arrhythmic death. This includes improvements in device capability, size, and reliability. The modern tiered-therapy ICD is capable of delivering antitachycardia pacing or shocks to terminate successfully nearly all sustained ventricular tachyarrhythmias (Figure 3). In addition, it provides backup bradycardia pacing and discrimination of supraventricular from ventricular arrhythmias. Recently, the dual-chamber ICD was introduced, providing physiological pacing and augmented diagnostic capabilities.

Secondary Prevention
Two relatively large and a smaller randomized trial have provided convincing evidence that ICD therapy is superior to class III antiarrhythmic drugs or β-blocker monotherapy in reducing mortality rates in patients with spontaneous, life-threatening arrhythmias (Table 1). These studies have generally included patients who survived a cardiac arrest caused by ventricular fibrillation or ventricular tachycardia (VT).

Antiarrhythmics Versus Implantable Defibrillators Trial
The Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial was terminated early, when patients randomly assigned to ICD therapy were demonstrated to be 31% (95% CI, 10% to 52%) less likely to die than those receiving antiarrhythmic drug therapy, mostly amiodarone, translating...
into an average life extension of 2.7 months.18 Thus, 88 patients need to be treated with an ICD for 3 years to prevent 10 deaths (11.3% absolute reduction). Initial analyses suggest that the incremental cost of an ICD is approximately $28 000 over 3 years or $125 000 per additional year of life.21 The early termination of AVID has at least 2 important implications. When a trial is terminated prematurely, the magnitude of benefit may be larger than had the study gone to its scheduled completion.22 The shorter average duration of follow-up may also have led to an underestimation of cost-effectiveness because much of ICD therapy cost occurs early on.23 Given the modest benefit of the ICD in AVID, analyses were undertaken to identify groups most likely to benefit. One found that the 61% of patients with EF values <0.35 had a marked (40%) relative reduction in the risk of death with ICD versus drug therapy, whereas patients with higher values did not significantly benefit.24 Similar to other trials (Table 1), AVID included relatively few patients with advanced heart failure, marked reductions in EF, or advanced age and has limited power to assess the relative efficacy of ICD versus drug therapy in these and other small subgroups.25

**Canadian Implantable Defibrillator Study**

The Canadian Implantable Defibrillator Study (CIDS) demonstrated a trend toward a lower risk of death with ICD therapy versus amiodarone (20% relative reduction, \( P=0.14 \)) over an average follow-up of 36 months.19 The reasons for the difference in ICD efficacy in CIDS versus AVID are unclear but may reflect differences in the duration of follow-up or patient characteristics. The 4.3% absolute reduction in mortality rates translates into treating 233 patients with an ICD to prevent 10 deaths. Initial analyses indicate that the incremental cost of an ICD is approximately $150 000 per life-year gained.26 Similar to AVID, patients in CIDS with EF values <0.35 significantly benefited from ICD therapy, whereas patients with better-preserved left ventricular (LV) function did not.27 It is estimated that selective use of an ICD for patients with EF values <0.35 lowers the incremental cost to less than $70 000 per life-year gained.26 Despite the lack of benefit from ICD therapy in patients with better-preserved LV function, they remain potential ICD candidates, and these analyses merely suggest that amiodarone is an appropriate option for these individuals.

**Cardiac Arrest Study Hamburg**

The Cardiac Arrest Study Hamburg (CASH) compared ICD with drug (amiodarone or metoprolol) therapy and found a trend toward a lower risk of death with ICD therapy (23% relative reduction; \( P=0.16 \)).20 The 8.0% absolute reduction in risk of death with ICD therapy translates into 125 patients needing to be treated for 3 years to prevent 10 deaths.

**Primary Prevention**

Two large randomized trials of ICD therapy versus conventional care in patients with no prior history of life-threatening arrhythmias have been published,28,29 as has a large trial in which ICD therapy was used in a nonrandomized fashion.30

**Multicenter Automatic Defibrillator Implantation Trial**

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) compared ICD therapy with conventional care, mostly empiric amiodarone, in patients with ischemic LV dysfunction (EF \( \leq 0.35 \)), asymptomatic nonsustained VT, and inducible, nonsuppressible sustained ventricular arrhythmias during programmed electrical stimulation.29 Most patients (93%) had nonsuppressible monomorphic VT. MADIT demonstrated that ICD therapy reduced mortality rates versus conventional care (54% relative reduction; \( P=0.009 \)) (Table 1). This mortality rate reduction appears larger than that observed in the 3 secondary prevention trials. However, because of fewer deaths in MADIT (\( n=54 \)) versus AVID (\( n=200 \)), CIDS (\( n=181 \)), and CASH (\( n=120 \)), the 95% confidence limits surrounding the estimate of ICD efficacy in MADIT are wide (18% to 74% reduction) and overlap with those of the secondary prevention studies.

An interesting observation in MADIT is that the annual mortality rate in the control group is higher than that observed in the secondary prevention trials (Table 1). Whether this reflects the small sample size in MADIT (ie, a chance finding) or other factors is unclear. It is important to note that all patients in MADIT had EF values \( \leq 0.35 \). Because patients with EF values <0.35 benefited from ICD therapy to a greater extent in CIDS and AVID, the inclusion of patients with marked LV dysfunction in MADIT may explain this observation. The average extension of life with an ICD in MADIT was 10 months. This large reduction in mortality rates (26.2% absolute) translates into needing to treat 36
patients for 27 months with an ICD to prevent 10 deaths at an incremental cost of $27 000 (95% CI, $800 to $68 200) per life-year.31 Similar to CIDS and AVID, MADIT patients with lower EF values benefited most from ICD therapy.32

It is unknown how many patients with ischemic LV dysfunction and nonsustained VT would need to be screened to identify 1 patient fulfilling all of the inclusion criteria, but is estimated to be large because these criteria are present in very few (<2%) post–myocardial infarction patients.33 Another concern in MADIT was the nonprotocol-driven use of antiarrhythmic drugs. For example, 23% of patients assigned to conventional therapy were not receiving antiarrhythmic drug therapy at last follow-up, and only 55% of patients were receiving amiodarone at that time. Because of these issues, MADIT alone does not provide sufficient evidence to support ICD therapy for the primary prevention of SCD.

Coronary Artery Bypass Graft Patch Trial
The Coronary Artery Bypass Graft (CABG) Patch Trial compared ICD therapy with usual care in 900 patients with EF values ≥0.36 and abnormal signal-averaged ECG recordings undergoing coronary artery bypass grafting (CABG).29 No significant reduction in mortality rate was observed with ICD therapy (relative increased risk, 7%; P = 0.6) over an average follow-up of 32 months, but a secondary analysis found that the ICD significantly reduced the risk of SCD.34 Despite attempting to identify a group of patients at high risk for SCD, most (71%) deaths in CABG-Patch were nonarrhythmic.34 Thus, the lack of benefit from ICD therapy appears related to a low risk of SCD. The reason(s) for the divergent results of MADIT and CABG-Patch will likely never be fully understood. Despite similar characteristics of the 2 populations, including EF values, MADIT patients had higher annual rates of death (Table 1). Whether this relates to different inclusion criteria, the impact of revascularization,35 or statistical chance is not known. The lack of significant benefit from ICD therapy in CABG-Patch highlights the need for restraint in use of ICD therapy for the primary prevention of SCD.

Multicenter Unsustained Tachycardia Trial
The Multicenter Unsustained Tachycardia Trial (MUSTT) compared antiarrhythmic therapy with best medical therapy in 704 patients with coronary artery disease, EF values ≥0.40, nonsustained VT, and inducible sustained ventricular

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**TABLE 1. Completed Trials of ICD Therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>Women, %</th>
<th>NYHA class &gt; II</th>
<th>Ejection Fraction</th>
<th>Follow-Up, mo</th>
<th>Annual Control Group Mortality Rate, %</th>
<th>Relative Risk Reduction,* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous arrhythmias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVID</td>
<td>1016</td>
<td>65±10</td>
<td>20</td>
<td>10%</td>
<td>0.35±0.12</td>
<td>18±12</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>CASH</td>
<td>228</td>
<td>58±11</td>
<td>20</td>
<td>17%</td>
<td>0.45±0.17</td>
<td>57±34</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>CIDS</td>
<td>659</td>
<td>64±9</td>
<td>16</td>
<td>11%</td>
<td>0.34±0.14</td>
<td>36</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Inducible arrhythmias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT</td>
<td>196</td>
<td>63±9</td>
<td>8</td>
<td>...</td>
<td>0.26±0.07</td>
<td>27</td>
<td>17</td>
<td>54</td>
</tr>
<tr>
<td>MUSTT</td>
<td>704</td>
<td>65±9</td>
<td>10</td>
<td>24%</td>
<td>0.28±0.08</td>
<td>39</td>
<td>13</td>
<td>51</td>
</tr>
<tr>
<td>No documented prior arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG Patch</td>
<td>900</td>
<td>64±9</td>
<td>16</td>
<td>...</td>
<td>0.27±0.06</td>
<td>32±16</td>
<td>8</td>
<td>7% increase</td>
</tr>
</tbody>
</table>

*Risk of death in ICD group vs comparison group(s).
arythmias during programmed electrical stimulation.\textsuperscript{30} Patients were enrolled from a pool of 2202 patients recruited at 85 centers in the United States and Canada over 6 years. Most (1435; 65%) of the 2202 patients did not have inducible ventricular arrhythmias and were not eligible for random assignment. Only 63 (8%) of 767 patients with inducible ventricular arrhythmias refused random assignment, strengthening the generalizability of the results. The 351 patients randomly assigned to electrophysiologically (EP) guided therapy underwent serial drug testing with randomly assigned antiarrhythmic agents. ICD therapy could only be used after failure of \( \geq 1 \) antiarrhythmic drug, and amiodarone could be tested only after \( \geq 2 \) failed drug trials. Similar proportions of patients assigned to this strategy were discharged with drug therapy (\( n=158; 45\% \)) versus an ICD (\( n=161; 46\% \)). Of the 158 patients discharged with drug therapy, most received a class I agent (26%). Amiodarone (10%) and sotalol (9%) were used in the remaining patients. \( \beta \)-Blockers were less frequently used in patients assigned to EP-guided therapy (29%) versus no antiarrhythmic therapy (51%). Over an average follow-up of 39 months, the risk of cardiac arrest or death attributed to an arrhythmia was significantly lower among patients randomly assigned to EP-guided therapy versus conventional care (27% relative reduction; 95% CI, 15\% to 47\%; \( P=0.04 \)). The absolute risk of death in patients assigned to EP-guided therapy was 6\% over 5 years. However, the benefits in terms of overall survival and the risk of arrhythmic death or cardiac arrest in patients in the EP-guided therapy group were limited to patients who received an ICD. The risk of death over 5 years was substantially lower in patients discharged with an ICD (24\%) versus drug therapy (55\%), translating into a 49\% lower relative risk. The large absolute reduction in the risk of death (31\%) translates into only 32 patients needing treatment with an ICD to prevent 10 deaths over 5 years. Drug therapy was not associated with a survival advantage compared with best medical therapy. MUSTT provides additional evidence of reduced mortality rates with ICD therapy in patients with ischemic LV dysfunction, ventricular ectopy, and inducible ventricular arrhythmias. Because ICD therapy was not randomly assigned, these results do not provide the same level of evidence as a randomized trial. However, the concordant findings of MUSTT and MADIT provide credence to the strategy of actively identifying patients with ischemic LV dysfunction and asymptomatic nonsustained VT to prescribe an ICD for patients with inducible sustained ventricular arrhythmias.

Less Common Disorders
Several recently published observational studies in patients with congenital long-QT syndrome (LQTS)\textsuperscript{36} and hypertrophic cardiomyopathy (HCM)\textsuperscript{37–40} provide support for the primary prevention of SCD in these populations. Because of the relatively low prevalence of these conditions, randomized trials offer a unique challenge in terms of their logistics and practicality. Thus, clinicians and patients may opt for reliable prospective information on the risk of death and modes of death among patients receiving conventional therapy in these populations to decide on the use or nonuse of ICD therapy. Although this approach has been extensively criticized, recent studies\textsuperscript{41,42} suggest that properly conducted observational studies can provide reliable estimates of therapeutic efficacy.

It is also important to acknowledge that current evidence precludes a definitive statement as to the relative benefit of ICD therapy in these populations (ie, lack of a class I indication). However, many of these individuals have class II indications (ie, no general agreement) for ICD use.\textsuperscript{43} Long-QT Syndrome
\( \beta \)-Blockers are considered by many to be the primary initial treatment strategy for patients with congenital LQTS, but much of the data regarding their use were collected 2 decades ago or more. More current information on the association of \( \beta \)-blocker use and the risk of cardiac events (death, cardiac arrest, or syncope) is available from the International LQTS Registry (\( n=869 \)).\textsuperscript{36} Initiation of \( \beta \)-blockade was associated with a significant reduction in the annual risk of cardiac events over 5 years (0.97\( \pm \)1.42 with versus 0.31\( \pm \)0.86 without \( \beta \)-blocker; \( P<0.001 \)). However, patients with prior symptoms who received \( \beta \)-blockers were significantly more likely to have recurrent cardiac events compared with asymptomatic patients (relative risk, 5.8; 95\% CI, 3.7 to 9.1). Despite \( \beta \)-blockade, it is estimated that 32\% (95\% CI, 27\% to 37\%) of symptomatic patients will have a cardiac event over 5 years, and 14\% (95\% CI, 7\% to 21\%) of patients with a prior cardiac arrest will have a recurrence within 5 years. Another study of patients treated with both a pacemaker and a \( \beta \)-blocker found that despite combined therapy, patients with a prior cardiac arrest had a high (31\%) rate of cardiac events, whereas patients without a history of cardiac arrest were at lower (14\%) risk.\textsuperscript{44} On the basis of these and other data, clinicians may elect to choose an ICD for LQTS patients with a prior cardiac arrest or in asymptomatic patients with LQTS and a worrisome family history.\textsuperscript{45} The presence of specific genetic mutations (eg, LQT 3) may provide prognostic information related to the risk of SCD\textsuperscript{45} but remains to be confirmed.

Hypertrophic Cardiomyopathy
Several recent observational studies provide information on the risk of death and modes of death in patients with HCM. Among 744 patients followed for an average of 8 years, 125 deaths occurred, 64 (51\%) of which were related to HCM.\textsuperscript{39} SCD accounted for 47\%, and heart failure accounted for 36\% of these. Another 14 patients survived a cardiac arrest. Thus, 6\% of the patients had SCD or an aborted cardiac arrest over 8 years. The average age of patients with events was <40 years, and most events (71\%) were in patients with minimal functional impairment (New York Heart Association class I or II). In a subset of these patients (\( n=480 \)) the magnitude of LV hypertrophy was shown to be an independent predictor of SCD.\textsuperscript{38} None of the 69 patients with a maximal LV wall thickness at any site \( \leq 15 \) mm had SCD in follow-up, whereas the incidence rates in patients with LV wall thickness values of 16 to 19, 20 to 24, 25 to 29, and \( \geq 30 \) mm were 2.6, 7.4, 11.0, and 18.2 per 1000 person-years, respectively. Another analysis suggests that marked LV hypertrophy alone is not sufficient to justify prophylactic ICD use,\textsuperscript{40} but marked LV hypertrophy plus \( \geq 1 \) other risk factor (family history of SCD,
syncope, chest pain, nonsustained VT, failure of systolic blood pressure to rise with exercise) does identify patients at high risk.\(^4^0\) Thus, clinicians may elect to use an ICD for the primary SCD prevention in patients with HCM and marked LV hypertrophy, especially those who are younger and who have little functional impairment and other risk factors. Specific genetic mutations (eg, troponin T) may provide prognostic information related to SCD risk,\(^4^6\) but this remains to be confirmed.

**Ongoing Large Randomized Primary Prevention Trials**

Although observational data may provide information on therapeutic efficacy similar to that determined in randomized studies,\(^4^1,4^2\) randomization guards against both observable and nonobservable biases that may misrepresent efficacy.\(^4^7\) Details of 2 large ongoing trials, the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) and the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), are outlined (Table 2).\(^4^8\) These and other studies will provide more definitive evidence on the efficacy of prophylactic ICD therapy in these populations.

**Indication Creep**

Given the intuitive appeal of the ICD, some clinicians have chosen to implant an ICD in patients sharing some but not all of the characteristics of the patients included in past trials (Table 1). Although it appears logical to extrapolate the findings of trials, knowing the characteristics of these populations may provide the best estimate of efficacy in other populations. Another criterion often applied is what would one do if it is “your mom.”\(^4^9\) These patients often have class II indications for ICD therapy, with disagreement among experts as to its value.\(^4^3\) Whether one chooses to adopt an approach that focuses on an individual versus a societal perspective depends on many factors, including resource availability and issues of access and follow-up. This is not a minor issue because recent data on ICD use show a marked difference in the United States versus other nations, with the former more representative of an “individual” approach and the latter a “societal” approach to the delivery of health care.

**Degree of Benefit**

If an individual’s risk of SCD could be determined with certainty, it would be possible and reasonable to provide definitive advice on the appropriateness of an ICD. Because individual risk cannot be determined, we estimate it from the average risk of “similar” patients. However, this may be misleading because of changes in concomitant therapy. Although \(\beta\)-blockers significantly reduce the risk of SCD in many populations, they were prescribed for <50% of patients in past ICD studies (Table 2). Likewise, although the benefit of ACE inhibitors in patients with LV dysfunction is clear, 25% to 50% of patients were not prescribed these agents. A post hoc analysis in AVID found that use versus nonuse of \(\beta\)-blockers had no effect on the impact of either ICD or amiodarone therapy.\(^5^0\) However, because the use or nonuse of these agents is nonrandom, it is difficult to know with certainty what their impact was on the results of these trials.

**Cost-Effective, Not Inexpensive**

Regardless of one’s philosophy related to the ICD and other costly interventions, a steadfast requirement is that the choice of an ICD over amiodarone or no therapy be based on the principle of a reasonable probability of success. This notion must be considered in terms of a broad perspective (ie, impact on mortality, quality of life, potential complications, cost). Although we label therapies as “cost-effective” if they are similar in cost to other interventions (eg, renal dialysis), it does not mean they are inexpensive. This is of particular relevance when we concurrently utilize multiple interventions in a single patient (eg, renal dialysis, CABG, ICD). Ultimately, because of the evolving face of health care delivery in North America and elsewhere, issues of cost will influence the practice of medicine. Furthermore, estimates of cost-effacy derived from clinical trials may not mirror efficacy in the real world.

**Alternatives to Current ICD Therapy**

Broad use of preventive therapies (eg, antithrombotic agents, \(\beta\)-blockers, lipid-lowering drugs, ACE inhibitors, smoking cessation) in patients with or at high risk for coronary heart disease would significantly reduce the burden of SCD, but is difficult to implement, and automated external defibrillators are currently of limited impact because of reduced availability. Moving away from a “one size fits all” approach to ICD therapy has been proposed as another means of reducing cost.\(^6\) This involves tailoring therapy, so that individuals requiring an ICD with advanced physiological functions would receive such a device (“Rolls Royce”), whereas those not requiring these features could be prescribed a simpler, less expensive yet fully functional device with restricted but
adequate detection and storage capabilities and the capacity to deliver up to 10 shocks (“Volkswagen”). Although this approach is appealing, it will require a major change in the attitudes of device manufacturers, in the prescribing patterns of physicians, and in patient expectations.

Summary

The ICD represents an important advance in the prevention of SCD, and there is great temptation to extend the indications for its use beyond what has been demonstrated. Compared with conventional antiarrhythmic drugs or best medical care, the ICD reduces mortality rates in certain patients at risk for SCD, those with ischemic LV dysfunction, and spontaneous18–20 or inducible life-threatening arrhythmias28,30 with the magnitude of benefit related to the severity of LV dysfunction.24,27 However, patients with ischemic LV dysfunction and an abnormal signal-averaged ECG undergoing CABG do not benefit from prophylactic ICD therapy.29 Thus, caution is required in extending the results of past trials to “similar” populations.

Although widespread use of ICD therapy for primary prevention of SCD is understandable, this approach is not without risk in terms of complications related to the initial implantation and subsequent revisions, alterations in quality of life and cost. Although it is reasonable and often necessary to extrapolate the findings of past studies, it is prudent to consider a reasonable probability of success, including assessment of SCD risk versus the risk of competing modes of death. Ongoing studies will help to define the role of the ICD for the primary prevention of SCD, and the enrollment of patients in these trials is encouraged. In the absence of a definitive answer, it seems prudent to maximize therapies previously demonstrated to be beneficial in reducing the risk of death and SCD and limit prophylactic ICD use to patients most likely to benefit.

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References


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