Introduction
During the last 25 years, remarkable technical and conceptual advances have occurred in clinical electrophysiology. The scientific foundation that underpins the everyday use of the implantable cardioverter defibrillator (ICD) involves more than the mere invention of a defibrillating device. The ICD was first demonstrated to be clinically useful in the early 1980s. At the same time, clinical epidemiologists were beginning to identify specific high risk groups of postmyocardial infarction patients who might be candidates for the ICD. While a broad series of observational studies in the 1980s quantified the impact of the ICD in comparison to other available therapies for high risk patients, there followed in the 1990s a decade of well designed clinical trials of the ICD.

Contributions from many sources explain the evolution of the ICD over the past 25 years. The ICD and its important role in clinical electrophysiology have embellished the reputations of its inventors, dominated the day-to-day careers of many electrophysiologists, and extended the lives of an ever increasing number of patients.

The Device
By the late 1960s, external cardiac defibrillation was acknowledged to be an effective means of terminating several abnormal cardiac rhythms including ventricular fibrillation (VF). The history of the ICD began at that time as well. Michel Mirowski came to the Sinai Hospital in Baltimore in 1969 with the idea of developing an automatic implantable defibrillator. The concept that he pioneered was “blind and immediate defibrillation treatment for cardiac arrest,” although the implanted device was considered to have some degree of “intelligence” built in. In a 1970 publication, Mirowski and his collaborator, Morton Mower, described the key elements of such a device. Based on their experience in the coronary care unit, it was clear that such a device must quickly recognize and treat VF with a unit that is small enough to implant in patients, yet still has long battery life. This was at a time when pacemakers were large and bulky.

In addition to the clinical activity in the coronary care unit, heart station and private practice, Mower and Mirowski worked in the hospital’s clinical engineering and animal facilities and by 1969 had designed, constructed, and tested a prototype device in dogs. Mirowski always believed that endocardial defibrillation was a viable concept, but it was years before such a lead system could be designed and used in clinical practice.

The first system design used a single transvenous lead in the right ventricle (RV) and a patch on the anterior chest wall with defibrillation achieved using 30 to 50 J, and indeed a variant of the superior vena cava (SVC) coil to apical patch was chosen for initial implantation. Later the lead design was changed to include a completely transvenous system consisting of an RV apical electrode with a second electrode in the SVC or right atrium (RA). The method of sensing ventricular fibrillation also evolved. Initially an RV pressure transducer was used to sense VF, and a drop in blood pressure triggered the device. This sensing method, while not unreliable, was considered by Mower and Mirowski to be more radical than an electrocardiographic feature, and the probability density function, which distinguished VF from sinus rhythm based on how much of the cardiac cycle is spent on the isoelectric line, was selected as a means of sensing VF.

By the mid 1970s, the initial short-term studies outlined above were confirmed in a study of 25 animals with long-term implanted devices. Subsequent studies in humans undergoing coronary artery bypass grafting demonstrated that intravascular defibrillation could be accomplished with energies of 15 J or less, which confirmed the earlier canine work. Over the period of a decade,
the key elements of successful defibrillation of clinical VF had extended from the inventors’ concept to the development of an implanted device that provided reliable sensing and defibrillation in a small volume unit. Despite these encouraging published results, there were prominent dissenters who stated that “the implanted defibrillator system represents an imperfect solution in search of a plausible and practical application.”

In September 1988, the Ventak P device featured multiprogrammable integrated circuits whose parameters could be changed by physicians. Rates could be programmed between 110 to 200 beats per minute and energies between 0.1 and 30 J. While the device itself was improved, its clinical role was not well defined in the mid-1980s as Eli Lilly had little experience with interest in medical technology.

The character of the co-inventors of the device also deserves comment. Michel Mirowski was an extremely focused and charismatic individual who was convinced of the correctness of the implantable defibrillator concept. Through force of will, and despite many setbacks, he insisted the project be completed. However, without Morty Mower, whose brilliant problem-solving skills made the device a reality, the ICD might have been delayed for decades or not done at all. Without the availability of a reliable ICD, electrophysiologists would have limited tools with which to treat survivors of or candidates for sudden death.

The Leads

The lead system used in the first human open chest implantations in the 1980s was the spring patch and apical cup. Soon the apical cup was replaced by an epicardial patch. After 20 cases in the second year, a two patch system was used. During the 1980s, research interest in bipolar cardiac defibrillation between two intracardiac coils (one distal (RV) and one proximal (RA or SVC)) continued. A series of design modifications resulted in the CPI Endotak lead. This was a single lead with proximal and distal shocking coils; it was first implanted transvenously in 1988 without thoracotomy.

More than any other feature, the development of stable, durable and biocompatible transvenous defibrillating leads has been responsible for the rapid adoption of ICD technology. Transvenous leads transformed the implantation procedure from a 4 to 6 hour open chest procedure with a 3% to 5% operative risk, to a far simpler procedure performed in the electrophysiology laboratory under conscious sedation. Recent randomized trials point to the benefits of the ICD in the very sickest patients (who have the lowest ejection fraction [EF]), but implantation procedures in such patients are possible because of the transvenous lead. Also, as indications for the ICD widen to include primary prevention in younger
patients, it is critical that leads incorporate features of stability over time for pacing, sensing, and defibrillation.

Another innovative idea that is currently under study is to create a leadless defibrillator. This would use subcutaneous patches and a high energy generator that would sense and defibrillate ventricular fibrillation. If feasible, such a unit would eliminate transvenous lead malfunction and, perhaps, expand the acceptance of the ICD.

**Evolution of ICD Systems**

There has been a steady and remarkable evolution of device technology that has resulted in greater patient safety and comfort. The first generation devices were designed only to recognize VF and treat it with a high energy shock.\(^2^1\) The second generation devices had bradycardia pacing capability and minimal programmability. The bradycardia pacing feature was important as approximately 15% of patients with first generation devices required separate pacemakers.\(^2^3\) ICDs in such patients could undersense clinical VF if the pacemaker spike was sensed by the ICD, inhibiting arrhythmia detection and an ICD shock.\(^2^2\) Second generation devices had limited telemetry and simply noted the number of shocks delivered. The third generation devices introduced in the early 1990s had much more flexibility. Besides bradycardia pacing, they introduced antitachycardia pacing and low energy shocking capabilities for treatment of VT, as well as defibrillation capability and more extensive programmability and telemetry.\(^2^2\) Antitachycardia pacing can convert up to 90% of hemodynamically stable VT and is more effective at slower cycle lengths, especially those >350 ms.\(^2^5\)\(^2^6\)

The concept of tiered therapy in a single device was introduced in the early 1990s in the so-called third generation devices. This concept described a progression of therapy for VT defined by the rate of tachycardia and lack of success of any prior therapy; tiered therapy devices were programmed to deliver bursts of antitachycardia pacing (ATP) followed by a low energy shock before going on to a high energy shock.\(^2^7\) Although low energy shocks can correct sustained VT, in most cases the same VT can be terminated by ATP. If ATP fails, shocks of \(\leq 5\) J also are typically unsuccessful to convert VT to sinus rhythm, but unlike ATP are painful to the patient. Thus, we frequently “skip” the tier of low energy shock, and program ATP followed by a shock strength with high probability of terminating VT.

The initial defibrillation waveforms were monophasic, truncated exponentially decaying pulses with a tilt of 65%.\(^2^8\) This was a satisfactory waveform for thoracotomy implantations but not for transvenous lead systems. The most important modification in the defibrillation waveform was the development of biphasic waveforms that switch the output polarity from the capacitor in mid-discharge.\(^2^9\) This innovation, introduced in 1993, resulted in lowering the defibrillation threshold (DFT) by 30% compared with monophasic shocks. DFTs were reduced to very low levels (6.3 J \(\pm\) 5.2 J in one study) using biphasic shocks.\(^3^0\) A parallel innovation has been the incorporation of the infraclavicular pulse generator itself as the active or “hot” can, which also reduces DFTs and is now routinely used in all pectoral implants.\(^3^1\) An added benefit of the lower DFT with biphasic waveforms is the increased safety margin for defibrillation, which has enabled the safe administration of antiarrhythmic drugs months or even years after initial ICD implant.

Careers were made by studying the deleterious effects of drugs such as amiodarone, which can increase the DFT in a monophasic waveform ICD to the point that VF cannot be terminated. Now, we rarely see a patient who receives an antiarrhythmic drug to treat VT yet has a high DFT. Of course, it is important to retest these patients to evaluate the effect of drugs on VT rate.

The early ICDs were only able to sense ventricular rate and could not distinguish ventricular tachycardia from sinus tachycardia or atrial arrhythmias, especially atrial fibrillation. This simplistic approach resulted in nearly 25% of delivered shocks being inappropriate and not caused by ventricular arrhythmias.\(^3^2\) The ICD was often “blamed” for any inappropriate shocks; in reality, the programming physician was inappropriate in selecting incorrectly the cut-off values. A series of detection enhancements evaluating the onset and stability of the arrhythmia have improved sensing in the latest devices.\(^3^2\)

The evolution of the technical features of the ICD continues. The ICD generator will continue to miniaturize and may become as small as 20–25 cc. More complicated features are under study. These include the use of various metabolic or electrophysiological sensors that might herald the development of a cardiac arrhythmia before it occurs and use either pacing maneuvers, pharmacological agents, or modulation of autonomic activity to prevent an ICD discharge.\(^3^3\)\(^3^4\) Recognition of a problem could lead to a pacing maneuver, drug infusion (through a port in one of the intracardiac leads and with a reservoir possibly in the generator), or both, and hopefully would prevent or treat the problem. All of this would be programmed by the physician, and the device could use artificial intelligence to “learn” and change parameters as needed. Appropriate data would be sent wirelessly to the physician as directed. These treatments would
occur seamlessly and provide peace of mind for the patient.\textsuperscript{33,34}

\section*{Identification and Treatment of High Risk Arrhythmia Patients in the 1980s}

In the late 1970s and early 1980s electrophysiology was transformed from a descriptive extension of electrocardiography, focused on verifying by intracardiac electrograms the interpretation of surface electrocardiograms, to one that has a critical role in the management of high risk patients. A number of research interests converged over a short period of time in the early 1980s including an interest in the mechanisms and clinical course of patients who died suddenly, an understanding of the ventricular arrhythmias which could be provoked in the closed environment of the electrophysiology laboratory, and the availability of pharmacological agents to treat these induced rhythms.

In the United States there are 350,000 to 450,000 out-of-hospital cardiac arrests per year.\textsuperscript{35} Data from the 1970s and early 1980s showed that sudden death survivors who were untreated had a one year subsequent sudden death mortality of 30\%,\textsuperscript{36,37} and a 5 year total mortality of 70\%–80\%.\textsuperscript{38–40} Empiric drug treatment without serial drug testing carried a one year recurrence rate of 20\%–30\% and a 5 year mortality of 70\%–80\%.\textsuperscript{36–40} Thus, it was clear that alternative treatment methods were necessary since empiric antiarrhythmic therapy was unsuccessful.

In the early 1980s, high risk populations such as patients after myocardial infarction, those with unstable angina, or heart failure were studied and followed in an effort to quantify risk and establish the clinical variables that predict high risk. The features that define high risk include measures of left ventricular dysfunction, abnormal ventricular arrhythmias, and abnormal autonomic nervous system function.\textsuperscript{41} Over 20 years ago left ventricular ejection fraction (LVEF) was shown to be the strongest predictor of death after myocardial infarction.\textsuperscript{41} Four large studies compared mortality in patients with an EF less than and greater than 40\%,\textsuperscript{42–45} In patients who have an EF $<$0.40, the mortality rate at 2 years after infarction is 21.5\% compared with 7.6\% in patients with an EF $>$ 40\%. The risk of a low EF is hyperbolic, with the mortality rate sharply increasing as the EF falls: an EF of $<$20\% predicts a one year mortality of 50\%.\textsuperscript{46} In the thrombolytic era, low EF postinfarction remains a powerful predictor of long-term mortality.\textsuperscript{47} These studies influenced patient selection criteria for the ICD primary prevention trials of the 1990s.

Additional data from these studies emphasized the prognostic importance of ventricular ectopy.\textsuperscript{42–45} As premature ventricular contraction (PVC) frequency increases to between 1 and 10 PVCs per hour, the mortality curve rises sharply to rates approaching 20\%.\textsuperscript{41,42,46} Complex ectopy, pairs or runs of nonsustained VT, are predictors of death independent of the number of PVCs. The strongest predictor of subsequent mortality is nonsustained VT, but this only occurs in 10\% of the postinfarction population. Studies in patients in the post-thrombolytic era confirm the risk of greater than 10 PVCs per hour in the first 6 months postinfarction. In the post-thrombolytic period, the presence of nonsustained VT has dropped to 6\%–8\% of all patients.\textsuperscript{49}

Early work from the University of Pennsylvania electrophysiology group in the late 1970s demonstrated that the induction of monomorphic VT was a reproducible and specific response to catheter based programmed stimulation, which supported reentry as the underlying mechanism.\textsuperscript{50} In the late 1970s and early 1980s, electrophysiologists in major centers routinely used programmed stimulation in patients with the highest risk of recurrence (i.e., survivors of clinical VT or VF) to stratify risk of recurrence. A large number of observational studies were performed to document the clinical utility of pharmacological therapy guided by programmed stimulation but, in fact, had variable results.\textsuperscript{51} In general the invasive approach in the postevent population was reasonably successful at predicting lack of recurrence (typically 80\% to 100\% effective) in an inducible patient, but a drug regimen that prevented recurrence could be found in only a minority of patients. Thus, most patients were nonresponders and at ongoing clinical risk. If discharged on a regimen that was not protective in the electrophysiology lab, the annual mortality was at least 30\% at 20 months.\textsuperscript{51} The limitations of this approach were most marked in the SCD survivors: up to 30\% of survivors had no inducible arrhythmias. This group of patients was one of the first to consistently receive ICDs.

Two other studies in the late 1980s had a major effect on electrophysiologists’ thinking about how to deal with the high risk patient. The Cardiac Arrhythmia Suppression trial (CAST) demonstrated a 2.5-fold increase in mortality in post-myocardial infarction (MI) patients treated with encainide and flecainide despite suppression of spontaneous ventricular ectopy.\textsuperscript{52} The continuation of the CAST trial with moricizine failed to show any benefit despite arrhythmia suppression.\textsuperscript{53} A meta-analysis of 10 additional studies that assessed the risks and benefits of antiarrhythmic therapy in 4,122 post-MI patients suggested that these agents probably shorten post-MI survival.\textsuperscript{54}

Finally, the brief era of surgery for ventricular arrhythmias in the early 1980s was
instructive in extending our understanding of the mechanisms of ventricular arrhythmias but was not widely applied clinically. Map-guided subendocardial resection was used in a few select centers in the 1980s, typically in patients with sustained VT and an aneurysm. The results of the operation were successful in that typically 70% to 98% of the patients were noninducible postoperatively. However, operative mortalities of 6% to 15%—even in highly experienced centers with highly skilled surgeons—were prohibitively high, especially as the transvenous ICD with its low operative risk became more widely available.55–59

**Early Results with the ICD (1980–1990)**

The first patient to receive an ICD had a previous MI and recurrent episodes of drug-resistant VT requiring resuscitation. After the first three implantations, a paper describing the initial results was published.60 In September 1982, the data from the first 52 ICD implantations were published.61 Patients in this study had survived two cardiac arrests despite antiarrhythmic drug therapy. During a mean follow-up of 14 months, 62 episodes of symptomatic tachycardia were terminated in 17 patients. In this very sick group of patients, the one-year sudden death mortality was 8.5% and all cause mortality 22.9% with the ICD.61 The clinical trial continued in two centers between 1980 and 1982 and then expanded to 40 centers until the FDA approved the ICD device in 1985. At that time approval was limited to patients with one episode of cardiac arrest or patients with recurrent ventricular arrhythmias that were inducible but not suppressed with conventional antiarrhythmic drugs.62 In January 1986, the Health Care Finance Administration released its coverage issuance for Medicare that reimbursed for the ICD only as a treatment of last resort.63 Also, arrhythmia inducibility was required initially, but was later rescinded in 1991 by the Office of Health Technology Assessment.64

In the late 1980s, a number of reports from large ICD implanting centers consistently showed a very low sudden death rate. The largest early published experience was from the Stanford group: 270 ICD recipients experienced a sudden death survival rate of 99% at one year and 96% at 5 years with the overall survival 92% at one year and 74% at 5 years.65 Other studies, as well as the registry maintained by CPI and the Bilitch multicenter registry, reported similar survival figures.66–77 Comparisons between different therapies was difficult, but it appeared that patient survival with the ICD was better than with competing therapies, including empirical amiodarone, EP directed therapy, and arrhythmia surgery.58,78–80 Many prominent investigators thought that the ICD should be considered best or gold standard therapy rather than therapy of last resort.

The late 1980s were a difficult time politically in the electrophysiology community as clinicians struggled to define the role of the ICD in clinical practice. The advocates of the ICD were under pressure to demonstrate the effectiveness of the ICD. The ICD device and its lead system were evolving quickly and a carefully designed randomized trial would have been difficult to design and accomplish. There were also many, including the inventors of the ICD, who considered such a randomized trial unethical in resuscitated cardiac arrest patients. Intense criticism of this position emerged from a variety of sources.81,82 The most compelling of these arguments was that any new device needs its efficacy proven by a randomized trial. Other arguments against widespread use of the ICD (and encouraging randomized trials) included the low ICD firing rate in some series, the concept that the sickest patients would die from their underlying cardiac disease anyway despite effective shocks, and the speculation that the high complication rate from an epicardial implantation cancels out any benefit of the ICD.83 This was a period of intense disagreement among prominent electrophysiologists with pro and con “camps,” each with their opinions but armed only with observational data to argue their point. Much of a given investigator’s opinion seemed influenced by his or her own medical center with its particular clinical skills and research interests. Finally, as the ICD implantation rate began to grow exponentially in the late 1980s, the cost implications of the therapy became a primary reason to undertake randomized trials of the ICD.


The early 1990s was a critical era in defining the appropriate role of the ICD in the treatment of the highest risk patients (Table I). Three trials—the Antiarrhythmics Versus Implantable Defibrillators (AVID), the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH)—were all conducted at roughly the same time. Taken together, the results of these trials support the use of ICD therapy for the secondary prevention of hemodynamically significant ventricular arrhythmias.

The AVID trial was National Heart, Lung, and Blood Institute supported and randomized patient groups thought by the AVID investigators to be at highest risk, viz., (a) those who had survived a cardiac arrest not associated with an acute myocardial infarction or transient cause, and (b) those with documented sustained VT with syncope or near
### Table I.
Randomized Clinical Trials of the ICD

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Control Therapy</th>
<th>History of Resuscitated Arrest (%)</th>
<th>Coronary Artery Disease (%)</th>
<th>Mean Ejection Fraction ± SD</th>
<th>Mean Follow-up (mths)</th>
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<tbody>
<tr>
<td><strong>SECONDARY PREVENTION</strong></td>
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<tr>
<td>AVID</td>
<td>1,016 pts resuscitated VF, sustained VT with syncope, VT with EF ≤ 0.4 and Sx</td>
<td>Amiodarone, sotalol</td>
<td>45</td>
<td>82</td>
<td>0.32 ± 0.73</td>
<td>18</td>
</tr>
<tr>
<td>CASH</td>
<td>288 pts resuscitated VF</td>
<td>Amiodarone, metoprolol, propafenone</td>
<td>100</td>
<td>73</td>
<td>0.45 ± 0.17</td>
<td>57</td>
</tr>
<tr>
<td>CIDS</td>
<td>659 pts resuscitated VF, sustained VT with syncope, sustained VT with EF ≤ 0.35 and Sx, syncope and VT</td>
<td>Amiodarone</td>
<td>48</td>
<td>83</td>
<td>0.34 ± 0.14</td>
<td>35</td>
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<tr>
<td><strong>PRIMARY PREVENTION</strong></td>
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<td>MADIT</td>
<td>196 pts with MI 3 weeks before entry: EF ≤ 0.36; NYHA class I, II, or III, Sx nonsustained VT 3 to 30 beats, inducible VT at EPS not suppressed by IV procainamide, 25 to 80 years of age</td>
<td>Antiarrhythmic drugs primarily amiodarone</td>
<td>0</td>
<td>100</td>
<td>0.26 ± 0.07</td>
<td>27</td>
</tr>
<tr>
<td>CABG Patch</td>
<td>900 pts with an EF ≤ 0.36 and + signalaveraged ECG; randomized in OR after CABG; &lt;80 years of age</td>
<td>Usual care</td>
<td>0</td>
<td>100</td>
<td>0.26 ± 0.06</td>
<td>32</td>
</tr>
<tr>
<td>MUSTT</td>
<td>704 pts with EF ≤ 0.40 and CAD, NYHA class I, II, or III, nonsustained VT &gt; 3 beats, inducible VT at EPS</td>
<td>No antiarrhythmics therapy</td>
<td>0</td>
<td>100</td>
<td>0.30</td>
<td>39</td>
</tr>
<tr>
<td>MADIT II</td>
<td>1,232 pts with MI ≥ 1 month; EF ≤ 0.3; NYHA I, II, or III, &gt;21 years of age</td>
<td>Usual care</td>
<td>0</td>
<td>100</td>
<td>0.23 ± 0.06</td>
<td>20</td>
</tr>
<tr>
<td>CAT</td>
<td>104 pts with EF ≤ 0.3, NYHA class II, or III; dilated cardiomyopathy &lt;9 months; CAD excluded by angiography; 18 to 70 years of age</td>
<td>Usual care</td>
<td>0</td>
<td>0</td>
<td>0.24 ± 0.07</td>
<td>66</td>
</tr>
</tbody>
</table>

Shown are the patient entry criteria used in the major published secondary and primary prevention ICD trials. Trial name abbreviations are as used in the text. VF = ventricular fibrillation; VT = ventricular tachycardia; Sx = symptoms; EF = ejection fraction; NYHA = New York Heart Association; IV = intravenous; MI = myocardial infarction; CAD = coronary artery disease; EPS = electrophysiological study; Note that the mean ejection fraction in the primary prevention trials was lower than in the postevent trials (Modified from Ezekowitz).\(^{92}\)
syncope and an EF ≤ 40%. The randomization scheme was very simple: patients were randomized to either the ICD or to amiodarone. Patients needing revascularization (10%) could only be randomized after the bypass procedure. The end point of the trial was total mortality with secondary endpoints of quality of life and cost. The pilot phase of the trial was initiated in June 1993 and enrollment was prompt. By March 1997, 1,000 patients had been enrolled and the study was terminated prematurely by the Data and Safety Monitoring Board (DSMB). At that time 1,016 patients had been enrolled. At a mean follow-up period of 18.2 ± 12.2 months, the accrued death rates were 15.8% ± 3.2% in the ICD group and 24% ± 3.7% in the drug group. Survival figures demonstrated a decrease in mortality of 39% at 1 year, 27% at 2 years, and 31% at 3 years in the ICD arm of the trial.84

The AVID patient population was virtually identical to those patients treated by electrophysiologically guided therapy in the 1980s. The mean EF was 31%–32%. Class III heart failure was present in only 7% of the ICD group and 12% of the drug group. Electrophysiological testing was not required, although 572 of the patients did undergo electrophysiological study. Of the patients studied, 384 (67%) had inducible arrhythmias, but at 1 and 3 years there was no difference in survival between the inducible and the noninducible groups.85

Subset analysis from the AVID study has provided additional insight into which patients benefit most from ICD therapy. Improved survival in the AVID trial was noted with the ICD only in patients with an EF of equal to or less than 35%, including patients with the lowest EFs. Patients with an EF over 35% derived no survival benefit due in large part to the overall better survival of the high EF arms of the trial.86 The carefully kept AVID registry included patients from certain arrhythmia populations not included in the main trial because their risk was thought low.88,89 The CIDS and CASH trials had similar design although the patient groups differed. CIDS had a modest 20% reduction of mortality in the ICD group compared with that of the amiodarone group.90 The CASH trial had a more complicated design and a long enrollment period, yet showed a mortality reduction of 37% in the ICD arm compared to the antiarrhythmic drug arm.91 A recent meta-analysis of the 1,963 patients included in these three trials found that ICDs reduced the relative risk for sudden cardiac death by 50% and provided a reduction in total mortality of 24% (Fig. 1). Based on these data, the 1998 ACC/AHA guidelines for ICD implantation made the main trial AVID patient groups a Class I indication for ICD implantation.93 This recommendation increased access to ICD therapy for patients regardless of the insurer and diminished the need for electrophysiological studies in selecting therapy.

### Era of the Prophylactic ICD Trials

In 1970, Mirowski and Mower speculated that the automatic defibrillator "might be implanted on a permanent basis in selected patients with coronary heart disease identified as belonging to a high risk population."94 Although opposed to postarrest trials on ethical grounds, they embraced the...
concept of randomized trials for patients at high risk before cardiac arrest—namely, primary prevention. Nearly 20 years later a series of prophylactic ICD trials were designed by investigators such as Bigger and Moss whose research interests were associated more with risk stratification rather than invasive electrophysiology. They used risk stratifiers from other studies of the 1980s including low EF and nonsustained VT. These trials were conceived and initiated years before any secondary prevention trial suggested a survival benefit for patients protected by an ICD. (Table I, Fig. 1)

The most interesting and controversial of these trials was the Multicenter Automatic Defibrillator Implantation Trial (MADIT). The conceptual framework of this trial arose from the known risk of nonsustained VT and a low EF in postinfarction patients. This risk model was verified by a study showing that if such patients had inducible VT and were not suppressed by an arrhythmic drug in the electrophysiology laboratory, they had a high risk of death.94 The MADIT trial enrolled patients with coronary disease, a low EF (≤ 35%) and nonsustained VT who could be induced at electrophysiologic study but not suppressed by procainamide in the electrophysiology laboratory.95 Patients were randomized to either conventional drug therapy, largely amiodarone, or to an ICD. During the course of the trial, there were 39 deaths in the conventional arm and only 15 deaths in the ICD arm. At 4 years, only 51% of the conventional group patients were alive. Also, 60% of the MADIT patients received a shock at 2 years confirming the protective effect of the ICD.95

The degree of risk reduction, 54% at 2 years, was anticipated in the design of the study; however, controversy about the design of the study quickly arose.96 There was no registry of screened patients as in AVID; a high percentage of patients discontinued their amiodarone, and there was disproportionate use of β-blockers in the ICD arm. The electrophysiology community did not adopt this study in everyday practice because of concerns regarding the data as well as cost implications. The general consensus was that more data were needed to support the MADIT findings. Despite these concerns, the ACC/AHA guidelines in 1998 gave the MADIT indication Class I status.93

The MADIT results received unexpected support when the results of the Multicenter Unsustained Tachycardia Trial (MUSTT) were published.97 This trial assessed the role of electrophysiologic testing in choosing appropriate therapy in a population similar to MADIT. Patients with coronary disease and an EF ≤ 40% with nonsustained VT who could be induced at electrophysiologic study were randomized to electrophysiologically guided therapy or to placebo. At the conclusion of the study approximately 45% of the inducible patients were discharged taking a drug thought to be effective: the nonresponders received an ICD. Because of the large number of patients in MUSTT, there were enough ICD patients to compare the MUSTT results to the MADIT results. The risk of death over 5 years was substantially lower in patients discharged with an ICD (24%) versus drug therapy (55%), which represents a 49% lower relative risk. The MUSTT patients who received an ICD after failing all drugs had a survival rate comparable to the ICD arm of MADIT.98

A subsequent analysis of the MADIT data showed that all of the survival benefit of the ICD was in patients who had an EF ≤ 26%.99 The MADIT investigators incorporated this observation, plus a desire to simplify the screening process, into the design of MADIT II.100 This trial was very simple in design; it randomized stable postinfarction patients with an EF ≤ 30% to either an ICD or no ICD. There was no arrhythmia requirement and no electrophysiological study. A total of 1,232 patients were randomized to an ICD or best medical therapy in a 3:2 ratio. The mean EF in this trial was 23% compared to 25%–27% in MADIT I. Nearly 70% were treated with ACE inhibitors and β-blockers, a much higher proportion than in MADIT I. Nonetheless, in this well treated patient group with advanced heart disease, the ICD reduced mortality by 31% (19.8% mortality in the conventional arm versus 14.2% in ICD arm). When studied independently in randomized trials, the absolute contribution of the ICD to reduction in all cause mortality in this patient group was larger than with other proven therapies such as β-blockers, CABB, or ACE inhibitors.101

Therefore, in all three major primary prevention trials in postinfarction patients, MADIT, MUSTT, and MADIT II, the use of the ICD reduced mortality respectively by 54% (at 27 months), 55% (at 39 months), and 31% (at 20 months) compared with standard medical therapy. This reduction in mortality is greater than the risk reduction noted in the secondary prevention trials—AVID, CASH, and CIDS—in which the mortality reduction was 31% (at 3 years), 28% (at 3 years), and 20% (at 3 years), respectively. The MADIT II indication was given a Class IIa indication in the 2002 revision of the ACC/AHA ICD guidelines.102 Using the data from the randomized clinical trials, a treatment algorithm can be constructed to help guide therapy in any given patient (see Fig. 2).103

Not all patient groups studied in recently completed ICD trials have shown a benefit for the ICD. The most surprising of these was the CABG-PATCH trial, which randomized low EF patients undergoing CABG surgery to either an ICD or no
Figure 2. The results of the primary and secondary ICD trials simplify the treatment of high risk patients with ventricular arrhythmias. This treatment algorithm summarizes an approach to each patient subgroup based on trial data. The recommendations are all either Class I or Class IIA indications based on the most recent ACC/AHA guidelines. These recommendations indicate at least one reasonable option for each patient subgroup and are not a substitute for sound clinical judgment. Future trial data may modify these recommendations. AA = antiarrhythmic; CAD = coronary artery disease; CM = cardiomyopathy (dilated); EPS = electrophysiologic study; Amio = amiodarone; EF = ejection fraction; PVCs = premature ventricular complexes; Rx = therapy; Sxs = symptoms; VT-NS = nonsustained ventricular tachycardia; VT-S = sustained ventricular tachycardia; RFCA = radiofrequency catheter ablation; ICD = implantable cardioverter defibrillator. Numbers reflect trial data supporting each recommendation: (1) AVID/CASH/CIDS; (2) MADIT I/MUSTT; and (3) MADIT II.

ICD. The defibrillator did not benefit mortality in the ICD arm of this trial. Mortality was 18% at 2 years and only 13% if one excludes operative mortality. Patients with a two year mortality of under 20% have little chance of benefitting from ICD therapy.

A major unanswered question is the usefulness of the ICD as primary prevention for SCD in patients with nonischemic dilated cardiomyopathy. Recent data from two major trials have shown no benefit from the ICD compared to best medical therapy or amiodarone. However, the results of the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial presented at the 2003 Scientific Sessions of the American Heart Association, clearly showed a survival trend favoring the ICD. Other ongoing trials involving dilated cardiomyopathy patients hopefully will clarify this issue. This patient group may have a lower mortality rate than expected compared to ischemic patients, perhaps due to an additional survival benefit of ACE inhibitors and β-blockers. There are other patient groups at significant risk of SCD that have not been subjected to randomized trials. These are patients groups often treated as ACC/AHA Class IIb indications for an ICD including those with Brugada syndrome, the long QT syndrome, or hypertrophic cardiomyopathy. If such patients have had cardiac arrest, then an ICD is generally implanted. However, often these patients are asymptomatic yet come from a family with history of sudden death or have had prior syncope but no documented arrhythmia. Preliminary data suggested that the use of the ICD in such populations is warranted.

Challenges and Future Directions

Data from the clinical trials showed that device therapy is expensive due in large part to the high cost of the ICD itself. A recent analysis suggested that in the AVID trial the incremental cost-effectiveness of the ICD compared with drug therapy was $66,677 per year of life saved in post VF patients. In MADIT, which had a more substantial risk reduction due to the ICD, the cost was $25,000 per life year saved.

The number of patients eligible for ICD implantation is large and growing. Some 300,000 new patients with LV dysfunction and coronary disease present in the United States each year. The number of ICDs implanted is growing at about 20% per year. Analysts expect that in 2003 nearly 130,000 new ICDs will be implanted worldwide. There is marked variability among countries in ICD implantation rates. In the United States there are 185 ICDs implanted/million population; in Western Europe 31 ICDs are implanted per million population and in Japan, 8 per million.

It is clear that the recent evolution and acceptance of cardiac resynchronization therapy (CRT) in patients with NYHA Class III and IV heart failure will further accelerate the growth rate of the ICD. The recently completed COMPANION trial showed that CRT therapy implanted with an ICD, reduced mortality by 40% in a low EF population (≤35%) with heart failure and a QRS ≥120 ms, while CRT alone reduced mortality by only 20% compared with the control population. Thus, based on both the MADIT II and COMPANION data, most patients who qualify for a CRT device will likely receive it with an ICD.

The DAVID trial evaluated the effect of ICD bradycardia programming on a composite endpoint of heart failure hospitalization and mortality. Patients had pacemakers programmed to either no pacing or to DDD pacing. Of the pacing group, 59% received continuous RV pacing and incurred...
a 39% increase in the one year risk of hospitalization or death.\textsuperscript{119} This shows that RV pacing itself worsens outcome and may explain in part the increase in heart failure in MADIT II. This observation will likely mean that any long-term ICD patient with substantial LV dysfunction who relies on RV pacing will be considered for CRT in addition to ICD whether or not heart failure is present.

A 15-year era, between 1988 and 2003, of randomized clinical trials of the ICD in high risk patient groups is concluding. A few more select patient populations will be studied in randomized trials in the future, such as patients with dilated cardiomyopathy and syncpe. Yet there are no other major patient populations at high risk who are unstudied using current stratification techniques. We need to develop better noninvasive tools—perhaps including genetic and neurohumoral markers—to identify the patient populations with low EF who may benefit from ICD, but to date this promise is unrealized.\textsuperscript{120,121} The prophylactic ICD trials have all shown that mortality risk is associated with a low EF (≤40%) in coronary artery disease patients and that other risk stratifiers including nonsustained VT, the signal average ECG, and electrophysiological study add little.

A remaining clinical challenge is to assure that patients who meet criteria for an ICD actually receive them.\textsuperscript{122} The uncompleted research challenge for the prevention of sudden death is to identify and protect a larger number of patients at risk in the general population but who do not have any of the well studied risk factors of the 1980s.\textsuperscript{123} The ICD is now regarded as everyday therapy for large groups of patients in hospitals of every size around the world. It will be the core therapy for groups of patients identified by new techniques as being at risk for sudden death and a component of any implantable device to treat heart failure. The evolution and acceptance of the ICD over two decades is comparable to that of the other building blocks of clinical cardiology including pacing, interventional cardiology, and echocardiography. This therapy is unique, however, in that its inventors—Mirowski and Mower—envisioned its importance 10 years before the first device was implanted and 30 years before clinical trials established its efficacy.

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References


