Sudden cardiac death (SCD) is among the most common causes of death in developed countries throughout the world. It is estimated that more than 3 million people die yearly from SCD, with a survival rate of less than 1%. In the United States, the Center for Disease Control recently estimated an annual incidence of 450,000 sudden deaths, with a survival rate of approximately 5%, although this probably is an overestimation. Although there has been a reduction in total cardiac mortality from 728,115 in 1989 to 719,456 in 1999, the percentage of deaths that are sudden has actually increased from 38% to 47%. The increase was greatest in women older than 65 years of age, from 56.3% to 63.9%. This has resulted primarily from an increase in out-of-hospital sudden deaths. There is a comparable incidence of SCD and survival rate in Western Europe. The magnitude of this problem can be understood by noting that SCD accounts for more deaths each year than the total number of deaths from AIDS, breast cancer, lung cancer, and stroke (Figure 1). Unfortunately, it is the first presentation of cardiac disease in 33% to 50% of patients and is 3 times as common in men than in women.

Coronary artery disease, with or without myocardial infarction, is by far the most common underlying disease for SCD in the western world, being responsible for approximately 75% of all SCDs. Cardiomyopathies (dilated and hypertrophic) and primary electrical heart disease account for most of the remainder. The two most important risk factors for SCD (ie, those with highest predictive value) are left ventricular ejection fraction (LVEF) less than 40% and clinical congestive heart failure. These are followed by significant ventricular arrhythmias (particularly nonsustained ventricular tachycardia [VT] or frequent ventricular premature complexes [VPCs]), ischemia, and left ventricular hypertrophy. The risk of mortality related to ejection fraction is nonlinear, with a marked increase beginning when the LVEF falls below 40%. The mortality in heart failure is bimodal. As one goes from class I to class IV heart failure, there is an increased annual risk of total mortality, whereas there is a decreased risk of SCD. Thus, in class II patients, more than half will die suddenly, whereas in patients with class IV heart failure, 10% to 40% will die of a cardiac arrhythmic event. The role of coronary artery disease and ischemia can never be underestimated. It has been known for nearly 20 years that surgical revascularization decreases the risk of SCD as well as total mortality in patients with 2- and 3-vessel disease, particularly those who have low ejection fractions.

The relationship of SCD to genetic abnormalities is under intense investigation. Although inherited disorders of lethal arrhythmias have been recognized, they make up a small proportion of SCDs. These include the long-QT syndromes, Brugada syndrome, and exercise-induced polymorphic VT. Specific genetic defects in ion channels or intracellular calcium handling have been identified. Mutations in cytoskeletal, contractile, and structural proteins also have been associated with SCD. What is evident is that genetic abnormalities alone cannot explain the occurrence or timing of SCD. Multiple factors regulate gene expression and function, including intracellular signaling proteins and environmental factors. Thus, phenotypic variability with the same genotype is commonly manifested by incomplete penetrance (eg, absence of long QT on ECG) or clinical course (eg, absence of arrhythmias). Just as disturbing is the fact that the same phenotype may be produced by several different genotypes (eg, long QT). The clinical problem in understanding the genetic basis for SCD is that it is a phenotypic expression of multiple factors. The observation that men die more often of SCD than women and that there is a familial tendency to SCD should promote more studies of the underlying molecular mechanisms for VT and ventricular fibrillation (VF). Understanding the mechanisms of the final common pathways of SCD would allow a better understanding of the specific interactions of proteins and external factors on the genetic substrate of individual patients.

**Pathophysiology of SCD**

The pathophysiology of SCD involves interaction of a triggering event and an abnormal substrate that induces electrical instability and VT that degenerates into VF. In fact, frequent VPCs (≥10 VPCs/hour) or nonsustained VT in the absence of structural heart disease are benign. Even in the presence of structural heart disease, they are a poor predictor of SCD (positive predictive value of ≈15%). If one is “fortunate enough” to record events during an episode of cardiac death, ventricular arrhythmias will be found to be responsible for 80% to 85% of cases. The most common misconception is that SCD is caused by a massive heart attack. Acute infarction is present in only 20% of the cases. SCD associated with...
bradyarrhythmias (15%) usually represents end-stage heart failure and a form of electrical-mechanical dissociation that is not reversible. Most commonly, SCD is caused by the onset of a rapid monomorphic VT that degenerates into VF. Less frequently, SCD is initiated by polymorphic VT/VF directly. In only a few cases, ST-segment changes suggestive of ischemia precede the initiation of the terminal event. Polymorphic ventricular arrhythmias are the most common initiating events in patients with ion channelopathies as well as in patients with pure hypertrophy without overt evidence of scar tissue. Whether there are common underlying molecular mechanisms to all forms of lethal arrhythmias is unknown. As noted above, certain individuals (such as those with male gender or positive family history) seem more predisposed to SCD. Understanding why this happens could unravel the final common molecular mechanism of lethal arrhythmias.

Prevention of SCD

Early attempts at preventing SCD were directed at suppression of ventricular ectopy. It took many years before doctors realized that the treatment of asymptomatic VPCs and nonsustained VT was not only inappropriate but dangerous. The debate finally ended with the Cardiac Arrhythmia Suppression Trial (CAST), which demonstrated that patients with coronary artery disease and modest ventricular dysfunction given antiarrhythmic drugs (flecainide or propafenone) had a higher mortality rate than controls. Thus, physicians learned that a “clean” Holter monitor did not assure freedom from SCD and the presence of VPCs did not specifically predict its occurrence. During the 1980s, it became recognized that β-blockers could provide a reduction of SCD that was not just attributable to its antiischemic effects. The reduction of overall mortality and SCD was greatest in those patients who had depressed ventricular function and who were older than 65 years. In fact, of all the antiarrhythmic drugs, only β-blockers, and perhaps amiodarone (particularly in association with β-blockers), demonstrated the ability to reduce SCD. Class 1 and class 3 agents have been ineffective and in many cases proarrhythmic. More recently, it has been demonstrated that ACE inhibitors, angiotensin-receptor blockers, antialdosterone agents, aspirin, and statins can reduce cardiovascular mortality and sudden death. The mechanisms by which these therapies work is unclear.

Nonpharmacological therapy for the prevention of sudden death includes antiarrhythmic surgery, with or without revascularization, and implantable defibrillators. Antiarrhythmic surgical procedures to treat VT/VF were developed in the late 1970s by Guiraudon and colleagues and Josephson et al. These procedures, which involved map-guided subendocardial resection or substrate-guided (scar, abnormal electrograms) exclusion of arrhythmogenic tissue from normal tissue, resulted in remarkable freedom from sudden death and a significant (>90%) reduction of recurrent VT. These procedures unfortunately lost their appeal because of a relatively high mortality and, more importantly, because of the development of the implantable cardioverter-defibrillator (ICD). Mirowski et al deserve credit for the development of the ICD, the use of which has exploded since its introduction more than 20 years ago. The initial devices were large, required thoracic surgery, and were nonprogrammable but could reliably convert VT/VF to sinus rhythm. For the past two decades, ICDs have become miniaturized and pectorally implanted with transvenous leads; use newer and more effective waveforms; are multiprogrammable, allowing for tiered therapy (antitachycardia pacing, low energy shocks, high-energy defibrillation shocks); have dual-chamber pacing capability; and, most recently, have incorporated biventricular pacing in patients to improve heart failure as well as to defibrillate the heart.

Although early studies showed that ICDs could uniformly terminate VT/VF, it was with development of the pectorally implanted device using transvenous leads in the early 1990s that the use of ICDs grew rapidly (Figure 2). It was not, however, until the landmark randomized controlled trials Antiarrhythmics Versus Implantable Defibrillators (AVID) and Canadian Implantable Defibrillator Study (CIDS) were reported in 1997 and 1998 that the device became widely accepted. These studies demonstrated that the ICD produced an approximate 30% reduction in relative risk of SCD in patients with prior sustained malignant ventricular arrhythmias. Unfortunately, the absolute benefit in each study was ≤7% per year. This was expensive, yielding an approximate cost per year of life saved approaching $125 000, a value much higher than usually accepted as being cost-effective. Nevertheless, with the publications of these secondary-prevention trials, ICDs became the therapy of choice for patients with prior cardiac arrest or hemodynamically poor tolerated VT.

The success of ICDs in preventing SCD in patients who had prior malignant arrhythmias led to its application for primary prevention. The first 2 randomized controlled trials for primary prevention were the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and Multicenter Unsustained Ventricular Tachycardia Trial (MUSTT). The former was sponsored by Guidant and the latter by the National Institutes of Health. Both trials were similar in that they required nonsustained VT in patients with a low LVEF (≤35% and ≤40%, respectively) for enrollment and inducible sustained tachycardia for randomization. In MADIT, there was a direct comparison between the ICD and the best
drug (usually amiodarone), whereas in MUSTT, it was randomization to a control group (ACE inhibitors and β-blockers) versus randomization to electrophysiologically guided therapy. The latter included randomized antiarrhythmic therapy, starting with drugs and ending up with ICDs in instances of drug failure or intolerance. In MUSTT, more than 190 patients received antiarrhythmic drugs and 161 received ICDs, whereas in MADIT, 101 received conventional antiarrhythmic therapy and 95 received ICDs. Both studies had problems with design. MUSTT was not a direct trial of ICD versus drugs, although the selection of drugs was randomized, and failure of drugs led to the use of ICDs. Notably, it had a control group as well as a registry including all patients who had no inducible VT. MADIT was limited by a smaller number of patients, absence of a registry for noninducible patients, absence of a registry of those patients in whom drug therapy was judged to be successful, and the failure to exclude patients who had a history of tolerated sustained VT. The inclusion of the latter patients may have been responsible for the nearly double inducibility rate of sustained VT in MADIT versus MUSTT. Nevertheless, the results of both trials were remarkably similar. Both showed 55% reduction in total mortality and 75% reduction in SCD. In MUSTT, there was an absolute reduction of SCD of 23%. This meant that 3 devices had to be implanted to save 1 life. Cost-effectiveness analyses of these studies suggested a cost of $16,000 to $22,000 per year of life saved, an extremely cost-effective result.

More recently, a simpler protocol was proposed by Guidant in the MADIT II study. More than 1232 patients were enrolled, 60% of whom received ICDs and 40% of whom received conventional therapy. The study was prematurely stopped after a follow-up period of 20 months, when a 30% relative reduction in mortality was demonstrated. The absolute reduction, however, was only 5.6%. This primarily was attributable to a reduction in SCD. Although the results of this study were immediately accepted by the Food and Drug Administration as a class IIA indication for ICD implantation, it led to significant controversy, primarily because of costs and applicability to the general population. There were many problems with this study that brought to light problems with all such trials in general (Table 1). These concerns were recently reviewed.31 The most important problem with these trials is significant enrollment bias—specifically, how and where patients are recruited and by whom. Most ICD studies enrolled patients either in the hospital, in the catheterization laboratory, or in a hospital-based office practice, which generally sees high-risk patients (eg, patients with known heart failure). The mortality rate of the control group in MADIT II probably does not clearly reflect the mortality rate of patients meeting enrollment criteria who are not found in these high-risk settings.

Interestingly, in MADIT II there was no significant effect on mortality in the first 18 months after infarction, the time period during which the highest frequency of deaths usually occurs. In fact, the greatest benefit was in people 10 years of age or older.

**Table 1. Issues in Trial Design**

<table>
<thead>
<tr>
<th>Patient selection—enrollment bias (site of patient enrollment and doctor responsible for enrollment)</th>
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<tr>
<td>Trial duration</td>
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<tr>
<td>What is too short?</td>
</tr>
<tr>
<td>What is too long?</td>
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<tr>
<td>Other factors to consider</td>
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<td>Impact of evolving technology</td>
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<tr>
<td>What hypothesis is being tested</td>
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<tr>
<td>Efficacy and efficiency of a therapy—critical for cost-effectiveness analysis</td>
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<tr>
<td>Alternative therapies</td>
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after infarction. This contrasts with results in MUSTT, in which those patients enrolled in an outpatient setting who survived more than 8 years after infarction showed little benefit of the ICD on their subsequent survival. This suggests that those patients who survive at least 8 years after infarction and are clinically stable are selected survivors and should be at lower risk. In addition, in MADIT II there was no comparison between β-blockers plus amiodarone, a combination that in the European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) led to a reduction in SCD. Moreover, MADIT II was stopped prematurely, so the mean follow-up period was less than 2 years. Whether the device will be more or less effective over time is unknown. By stopping trials prematurely, the survival benefits (only a few months) led to an estimated cost-effectiveness of $200,000 to $300,000 per year of life saved, an astronomical number that cannot be accepted by the government. Subgroup analysis demonstrated a progressive increase in effectiveness of the ICD as the QRS duration increased. In fact, there was little benefit derived in patients with a QRS of <0.12 seconds. If a QRS duration of 0.15 seconds was used as a cutoff, a marked reduction in SCD was observed, comparable to MUSTT and MADIT I. In this subgroup, the survival curves separated after approximately 1 year but continued to separate thereafter, with an absolute survival benefit of 36% and a relative risk reduction of 63%. As such, the government (Centers for Medicare and Medicaid Services [CMS]) elected to fund ICD implantation only in patients with QRS exceeding 0.12 seconds. This was done to reduce costs, because only approximately half of the patients met these criteria. By limiting the patient population, the CMS hoped to demonstrate cost-effectiveness similar to MUSTT and MADIT I. This controversy and the government’s response indicate the need to discuss cost-effectiveness as a criterion for funding ICDs. This is an issue not openly discussed but critical for the national economy.

New trials further augmenting this problem are those related to the use of cardiac resynchronization therapy. With this therapy, biventricular pacing is used to synchronize right and left ventricular contraction and enhance cardiac performance. Preliminary data have suggested that chronic right ventricular pacing, particularly in patients with abnormal left ventricular function, produces deterioration in function. The relationship of left bundle-branch block and increased QRS duration with cardiac mortality in heart failure patients has been long appreciated. Because ventricular contraction is dyssynchronous in left bundle-branch block, it was, therefore, logical to attempt to resynchronize ventricular contraction by simultaneous biventricular pacing to improve function. Preliminary studies have demonstrated that biventricular pacing in patients with severe heart failure improves clinical outcomes in terms of readmission for heart failure and quality of life. It is yet to be established that this form of therapy alone (ie, without an ICD) can prolong life. Recently, the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) study evaluated, in a randomized fashion, optimal pharmacological therapy, optimal pharmacological therapy plus cardiac resynchronization therapy, and optimal pharmacological therapy and cardiac resynchronization therapy with an ICD. The results of this study showed that the 2 biventricular pacing outcomes were better than optimal pharmacological therapy alone, but only optimal pharmacological therapy with resynchronization and an ICD significantly reduced mortality. This is not surprising, because this patient population is similar to the patients in MADIT II whom the CMS chose to fund (LVEF <30% and QRS ≥120 ms). The COMPANION study, however, did not require the cause of heart failure to be coronary artery disease with prior infarction. The exact role of biventricular pacing in subgroups of patients with heart failure needs to be evaluated. Some data suggest that biventricular pacing alone may not provide clinical benefits in patients with large anterior infarctions, and it is unclear whether those with biventricular failure are improved. An important question to address is the response to resynchronization in relation to right ventricular dimension and function. Whether the addition of an ICD to resynchronization will improve mortality is uncertain, because such patients frequently have class III or IV heart failure, and arrhythmic death is less common than death from pump failure or electrical-mechanical failure. Finally, there are several other trials that have not been completed that are trying to address the use of ICDs in patients with heart failure. The most prominent of them is the Sudden Cardiac Death in Heart Failure Trial (SCDHeFT). This study randomizes patients with clinical heart failure on stable medical therapy to (1) optimal pharmacological therapy, (2) optimal pharmacological therapy plus amiodarone, or (3) optimal pharmacological therapy plus ICD. The results of this study will address some of the problems with MADIT II, although it would not be surprising if the results were comparable to MADIT II, with a small absolute benefit but a 30% relative risk reduction.

What Is Missing?

Although it is clear that ICDs can convert malignant arrhythmias to sinus rhythm, this must be achieved at a reasonable cost to society. A major problem in making a big dent in the problem of SCD is that the randomized trials that have been undertaken only address a small proportion of the patients who die suddenly (Figure 3). A much larger percentage of people who die of SCD do not seem to be at high risk. Thus, using any expensive therapy for them would be grossly cost-ineffective, even if the cost of ICDs was reduced. The reason for this is simple. If the absolute risk is very low, the absolute benefit will be very small, even though one could potentially get statistically significant differences. Thus, applying therapies to a group of patients in whom the absolute incidence of sudden death is somewhere between 0.1% and 0.2% means applying costly therapy, with potential side effects, to many patients, the vast majority of whom will see no benefit. Thus, we need to identify high-risk patients among those who seem to be at low risk (Table 1). It is likely that the first step is to define a sequence of risk stratifiers that will identify patients who are at risk but in whom implantation of expensive devices will be cost-effective. The ECG may be a simple and useful tool. Left ventricular hypertrophy seems to be independently predictive of SCD, whereas
Better Screening Methods are an Absolute Necessity if the Largest Group of SCD Patients is to be Addressed.

<table>
<thead>
<tr>
<th>% Risk of SCD / year</th>
<th>Actual Numbers with SCD</th>
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<tbody>
<tr>
<td>General Population</td>
<td></td>
</tr>
<tr>
<td>High CAD Risk</td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;30, CHF</td>
<td></td>
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<tr>
<td>Arrest Survivors</td>
<td></td>
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<tr>
<td>High Risk post MI</td>
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Figure 3. Need for better screening methods to identify the largest group at risk. Adapted with permission from Myerburg and Castellanos.

increasing QRS width predicts total mortality. Identifying the amount of myocardium at jeopardy by ischemia is important; therefore, identifying multivessel coronary disease noninvasively would be useful. MRI and high-resolution computed tomography are modalities with great potential for achieving this. LVEF and a clinical evaluation of heart failure are easily obtainable. The signal-averaged ECG independently predicted total mortality but not specifically sudden death in MUSTT. T-wave alternans, heart rate variability, baroreceptor responsiveness, QT dispersion, and T-wave heterogeneity are other noninvasive tests that may be used singly, or more likely in combination with others, to select patients at risk. Holter monitoring to demonstrate ventricular arrhythmias and electrophysiological studies are proven risk stratifiers, but electrophysiological studies, in particular, are too expensive and invasive to be used initially.

TABLE 2. Need Better Way to Select Patients: Improved Methods of Risk Stratification

- 12-Lead ECG: QRS width, left bundle-branch block, left ventricular hypertrophy
- Amount of coronary artery disease: multivessel disease, extent of infarction
- LVEF: MADIT and MUSTT
- Clinical heart failure
- Signal-averaged ECG
- T-wave alternans
- Heart rate variability
- Baroreceptor responsiveness
- Holter—nonsustained ventricular tachycardia
- Electrophysiology study

The cost of all these may be worth it if fewer ICDs are implanted in patients who will not benefit.

Thus, it is likely that physicians will use a tiered approach to risk stratification to maximize selection of patients who are at high-enough risk so that devices could be implanted in a cost-effective manner. Obviously, reduction in the cost of such devices will make their application more cost-effective in a broader number of patients. Nevertheless, it is important to note that even if all high-risk patients were identified and appropriately treated, most patients dying suddenly would be unprotected.

Unresolved Issues

How to Control the Rapidly Growing ICD Population

The number of ICD implantations is growing exponentially (see Figure 2). It is predicted that in 2006 the number of implanted ICDs worldwide will be twice the present number. This will create problems in acute management in cases of device operation, device control, and reprogramming. Efforts are being made to develop home monitoring systems that wirelessly transmit device information from the home of the patient to the hospital or the doctor’s office. It is likely that in the future, wireless reprogramming will also be possible. These approaches may result in easier management of the growing ICD population. Before their widespread use, however, studies will be needed to assess their value and costs. Furthermore, issues related to medical-legal risk, interstate medical practice, and reimbursement will need to be resolved by state and national governments.

Role of the ICD After Cell Transplantation

There is presently great interest in transplanting cells into the hearts of patients who have lost or are in the process of losing an appreciable amount of cardiac tissue. Myoblasts as well as autologous bone marrow and embryonic stem cells are currently being evaluated for that purpose. A possible problem is the potential arrhythmogenicity of these cells because of their inability or reduced ability to transmit current to the surrounding native cells. This may facilitate the development of arrhythmias based on reentry or expose abnormal automaticity. The arrhythmogenicity may vary according to the type of cell used for transplantation. Studies will be needed to answer these questions and to establish when ICDs need to be implanted to protect the patient.

How to Protect the Population at Large

As already mentioned, only 10% of sudden cardiac arrest patients have a high-risk profile. Despite significant efforts to educate the public about SCD and cardiac resuscitation and, more recently, the application of automatic external defibrillators (AEDs), the number of individuals successfully resuscitated from cardiac arrest outside of the hospital remains small. It still remains exceptional to save more than 5% of those experiencing cardiac arrest. Most deaths occur at home, and 40% of people dying suddenly are unattended. The Postresuscitative and initial Utility in Life Saving Efforts (PULSE) initiative addresses these issues, identifying priorities and planning to improve results of resuscitation. Although availability of AEDs is increasing, immediate recognition of the event and initiation of cardiac massage and rapid availability of an AED and advanced care are essential to terminate ventricular fibrillation within 4 to 7 minutes. A
crucial step in the rapid management of these patients could be the development of wearable devices reliably able to recognize cardiac arrest, make an audible alarm, and transmit the location of the victim to the site of the nearest AED and advanced life support team. The development of these devices is a technical challenge, but it will improve survival. Of course, increasing the success rate of resuscitation will increase the number of people likely to benefit from implantation of an ICD. This stresses the necessity of lowering costs of devices and developing new methods for patient- and doctor-friendly control of their function.

Conclusions

The ICD has become established as an effective treatment for prevention of sudden cardiac death as (1) secondary prevention in patients successfully resuscitated from such an event or suffering from a life-threatening arrhythmia, (2) primary prevention in high-risk patients, and (3) an addition to biventricular pacing in patients at high risk for arrhythmic events. The indications and use of the ICDs will continue to grow, resulting in increasing discussions about costs and the necessity of better selection of ICD recipients through improved risk stratification. Improvement of results of resuscitation from out-of-hospital cardiac arrest remains an important challenge. Both better methods to recognize asymptomatic patients at risk (including genetic screening) and development of new technologies to shorten the time interval between cardiac arrest and the resuscitation effort are urgently needed.

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Implantable Defibrillators and Sudden Cardiac Death
Mark Josephson and Hein J.J. Wellens

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