By Michael R Lauer, MD, PhD

Clinical Management for Survivors of Sudden Cardiac Death

Sudden cardiac death is believed to affect as many as 400,000 people each year in the United States and is therefore an important public health problem. A common cause of sudden cardiac death is ventricular fibrillation. This article reviews the clinical and electrophysiologic aspects of sudden arrhythmic death and discusses current clinical management for survivors of sudden death. Particular emphasis is placed on the implantable cardioverter-defibrillator (ICD).

Introduction

Of the many possible cardiovascular causes of sudden death—arrhythmia, trauma, intracranial vascular catastrophes, and acute thrombosis or embolism affecting the heart or lungs—the present discussion is restricted to the arrhythmic causes and primarily to ventricular fibrillation. Not all episodes of ventricular fibrillation lead to death. As with atrial fibrillation, ventricular fibrillation may be both nonsustained and self-terminating or the patient may be rescued by bystanders or medical personnel who deliver a direct-current countershock to the patient's heart before irreversible cellular or organ damage intervenes. Nonetheless, sustained ventricular fibrillation inevitably leads to death within minutes unless the fibrillation is terminated. In contrast, monomorphic ventricular tachycardia may continue for many minutes, hours, or even days—depending on the rate of tachycardia—without development of clinically significant hemodynamic compromise. Although some cases of sudden arrhythmic death have been attributed to asystole or electromechanical dissociation, in general, these findings represent the natural evolution of untreated ventricular fibrillation and are not primary causes of sudden death.

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Definition and Epidemiology

Many investigators have grappled with defining sudden death. Torp-Pedersen, et al, suggest: "Since all death is (eventually) sudden and associated with cardiac arrhythmias, the concept of sudden death is only meaningful if it is unexpected, while arrhythmic death is only meaningful if life could have continued had the arrhythmia been prevented or terminated."[1:Abstract] The authors further state: "Any practical classification of death being sudden or arrhythmic is highly dependent on the quality of available data to ensure that the suddenness was unexpected and that life could have continued if the arrhythmia had been prevented or treated."[1:2545] Roberts has defined sudden death as "death which is nonviolent or nontraumatic, which is unexpected, which is witnessed, and which is instantaneous or occurs within a few minutes of an abrupt change in previous clinical state."[2:1410] For current purposes, sudden cardiac death shall be defined as death occurring within minutes from unexpected ventricular fibrillation or as ventricular tachycardia that rapidly (within seconds) accelerates to ventricular fibrillation and that if prevented or immediately terminated, would allow the patient to return to their previous level of functioning for an indefinite period. Given this definition of sudden cardiac death, the task of declaring an unwitnessed death as sudden or nonsudden remains difficult; in many cases, the "suddenness"—as well as the actual mode of death—may well remain a mystery.

Because of these uncertainties, accurately establishing the scope of the problem of sudden cardiac death also remains difficult. Sudden cardiac death is believed to affect as many as 400,000 people each year in the United States[3-5] and therefore is an important public health problem. The survival rate for out-of-hospital cardiac arrest is low: estimates range from 2% to 25% in the United States.[6,7] In addition, before the implantable cardioverter-defibrillator (ICD) or amiodarone became available, survivors of sudden cardiac death had a high rate of mortality after hospital discharge (24% mortality rate at one year; 34% at two years; 51% at four years) compared with an age-adjusted and gender-adjusted control group (20% mortality rate at four years) or for a similar control group discharged from the hospital after having acute myocardial infarction (34% mortality rate at four years).[8] Over the years, therefore, clinicians have been confronted by two issues: 1) how best to protect survivors of sudden cardiac death (ie, secondary prevention) and 2) how to identify on an a priori basis persons who have never had cardiac arrest but who are at highest risk for sudden cardiac death (ie, primary prevention).

Types of Arrhythmia Associated with Sudden Cardiac Death

For patients who have had an out-of-hospital cardiac arrest, the initial rhythm documented by para-

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medics seems to depend on the length of time between collapse of the patient and arrival of emergency medical personnel. When that time is unknown, the initial rhythm is found to be ventricular fibrillation in 40% of patients, asystole in 40%, electromechanical dissociation in 20%, and monomorphic ventricular tachycardia in 1%.[9] In contrast, when the time interval is known, the proportion of patients with ventricular fibrillation increases, whereas the proportion of patients with asystole decreases directly with increase of time interval between collapse and the first electrocardiogram (ECG). For example, when time between collapse and first ECG was between 12 minutes and 16 minutes, the initial arrhythmia documented was ventricular fibrillation in 71% of patients and was asystole in 29%; at between eight minutes and 11 minutes after collapse, the first arrhythmia documented was ventricular fibrillation in 88% of patients and was asystole in 12%; at between four minutes and seven minutes, the initial arrhythmia documented was ventricular fibrillation in 93% of patients and was asystole in 7%; and when <4 minutes had elapsed between collapse and first ECG, the initial arrhythmia documented was ventricular fibrillation in 95% of patients and was asystole in only 5% of patients.[10]

Contrary to common belief, ventricular fibrillation is not commonly precipitated by monomorphic ventricular tachycardia. First, a history of sustained monomorphic ventricular tachycardia is extremely uncommon in survivors of sudden cardiac death.[11] Second, monomorphic ventricular tachycardia is detected in only 16 (1.2%) of 1287 patients who had both cardiac arrest and treatment using an automatic external defibrillator within two-three minutes thereafter.[9] Third, among patients who had cardiac arrest while enrolled in a supervised cardiac rehabilitation program and who were resuscitated within 30 seconds, the initial arrhythmia documented was ventricular fibrillation in 92% of cases and was monomorphic ventricular tachycardia in only 8% of patients.[12] Fourth, most reports suggesting that monomorphic ventricular tachycardia precedes ventricular fibrillation in patients with cardiac arrest are based on Holter monitor tracings. This population is subject to statistical bias inasmuch as the patients were undergoing monitoring because of known, recurrent (usually ventricular) tachyarrhythmia (a condition atypical of patients who have cardiac arrest). For many patients, inspection of these Holter monitor tracings shows that instead of classic monomorphic ventricular tachycardia, the onset of tachyarrhythmia is actually ventricular flutter, polymorphic ventricular tachycardia, or frank ventricular fibrillation.[13-16] Further, because usually only one (or, at most, two) ECG leads are recorded for these patients, establishing monomorphic arrhythmia—even in the initial beats—is difficult. Even if the first few beats are known to be monomorphic, nearly all the Holter monitor tracings show rapid evolution to polymorphic arrhythmia or frank ventricular fibrillation.

Evidence from the electrophysiology laboratory also supports the conclusion that monomorphic ventricular tachycardia is uncommon in these patients as a presenting arrhythmia.[17] The Seattle investigators[17] found that in only 27% of patients who survived cardiac arrest, monomorphic ventricular tachycardia was induced during electrophysiologic testing. Patients with coronary artery disease who survived an out-of-hospital cardiac arrest also have a distinctly different clinical profile than do patients with a history of coronary artery disease and recurrent monomorphic ventricular tachycardia. Patients who survived sudden cardiac death have a lower incidence of remote myocardial infarction and left ventricular aneurysm and a higher ejection fraction than patients who have monomorphic ventricular tachycardia.[18] When seen at long-term follow-up, survivors of cardiac arrest who have implanted third-generation ICDs (which can store intracardiac electrograms) rarely have nonsustained or sustained monomorphic ventricular tachycardia.[19] In addition, patients with a history of recurrent monomorphic ventricular tachycardia only rarely present with ventricular fibrillation when seen at longterm follow-up.[18,20,21]

Taken together, these data strongly suggest that relatively few patients who suffer a cardiac arrest do so as a result of monomorphic ventricular tachycardia. Further, the finding of asystole or electromechanical dissociation in such patients usually indicates that a long time has passed since initiation of tachyarrhythmia and initial electrocardiographic documentation of the arrhythmia; stated differently, prolonged untreated ventricular fibrillation leads to cardiac quiescence. Patients who have cardiac arrest almost certainly present with ventricular fibrillation or a brief run (<15-20 seconds) of monomorphic ventricular flutter (ventricular rate >250 beats/minute) or polymor-

Table 1. Sudden cardiac death: causes and associated conditions

- Acute myocardial infarction
- Atherosclerotic coronary artery disease
- Coronary artery spasm
- Idiopathic dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Left ventricular hypertrophy
- Arrhythmogenic right ventricular dysplasia
- Congenital heart disease and coronary artery anomalies
- Valvular heart disease (primarily aortic stenosis)
- Congenital and acquired long QT syndromes (torsade de pointes)
- Antiarrhythmic drugs
- Severe electrolyte abnormalities
- Recreational drug use (eg, cocaine, methamphetamine)
- Infiltrative disorders (sarcoidosis, amyloidosis, hemochromatosis, myocarditis, cardiac tumors)
- Wolff-Parkinson-White syndrome
- Brugada syndrome
- Complete atrioventricular block
- Acute myocardial rupture/cardiac tamponade
- Massive pulmonary embolism
- Idiopathic ventricular fibrillation

phic ventricular tachycardia, either of which quickly develops into ventricular fibrillation. In addition, the patient population at highest risk for cardiac arrest appears to differ from patients who are at highest risk for recurrent monomorphic ventricular tachycardia. Consequently, research efforts directed at primary prevention of cardiac arrest should not necessarily target those patients at highest risk of suffering recurrent episodes of monomorphic ventricular tachycardia (eg, patients who have had spontaneous clinical episodes of monomorphic ventricular tachycardia or who have had monomorphic ventricular tachycardia induced in the electrophysiology laboratory).

Clinical Profile: Survivors of Sudden Cardiac Death

Occurring at a rate of 64% to 90%, coronary artery disease is the

Figure 1. Data from the β-Blocker Heart Attack Trial (BHAT) showing survival curve for patients who had a myocardial infarction and were treated with either a β-adrenergic blocking agent (propranolol) or placebo.

(Adapted and reproduced with the permission of the publishers and authors from: A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982 Mar 26;247(12)1707-14 Figure 1.)[30]

most common clinical condition associated with cardiac arrest.[22-28] In the experience of the Seattle investigators, the typical survivor of sudden cardiac death is a 60- to 70-year-old man with coronary artery disease (78% of cases) and a remote history of myocardial infarction (45% of cases).[11] Other clinical conditions have also been associated with sudden cardiac death (Table 1).

Role of Autonomic Nervous System in Sudden Cardiac Death

Enhanced sympathetic tone or increased sensitivity to sympathetic input—possibly with reduced modulating parasympathetic influence—may have a role in sudden cardiac death. Clinical studies[29-31] have shown that administration of β-adrenergic blocking agents soon after myocardial infarction results in reduced rates of sudden cardiac death, mortality, and recurrent infarction (Figure 1[30]). Patients with acute myocardial infarction who received β-adrenergic blockade during and after the acute phase of the infarct also had fewer episodes of early and intermediate-term ventricular fibrillation.[32,33] The role of the autonomic nervous system in triggering ventricular fibrillation in high-risk patients remains an intense area of ongoing research.

Risk Stratification and Predictors of Sudden Arrhythmic Death

Risk factors for sudden cardiac death include:

- Left ventricular dysfunction, in which those patients having the poorest left ventricular ejection fraction have the worst prognosis;
- Inducibility of monomorphic ventricular tachycardia by pro-

grammed electrical stimulation, especially in patients with reduced left ventricular ejection fraction;

- Ventricular ectopy, including single ventricular premature depolarizations (>10 ventricular premature depolarizations/ hour) and asymptomatic nonsustained ventricular tachycardia, in the presence of left ventricular dysfunction;
- Presence of late potentials on signal-averaged electrocardiogram;
- Reduced variability of heart rate;
- Abnormal baroreceptor sensitivity.

Severity of left ventricular dysfunction is the strongest predictor of total (sudden and nonsudden) cardiac mortality. According to investigators for the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study,[34] left ventricular ejection fraction <40% is a sensitive and specific predictor of sudden cardiac death. Left ventricular ejection fraction <30% is associated with a 3.5-fold increased chance of dying.[35-37] Inducibility of monomorphic ventricular tachycardia by programmed electrical stimulation in the presence of reduced left ventricular function is well established as a powerful predictor for recurrence of sudden cardiac death.[17] For example, survivors of sudden cardiac death who had ejection fraction >30% and in whom monomorphic ventricular tachycardia could not be induced at electrophysiologic study had a 2% risk of recurrence of sudden death or ICD shocks (used as a nonfatal equivalent of sudden death) at one year and had an 11% risk of recurrence at two years, whereas the risk of recurrent sudden cardiac death or ICD shock was 23% at one year
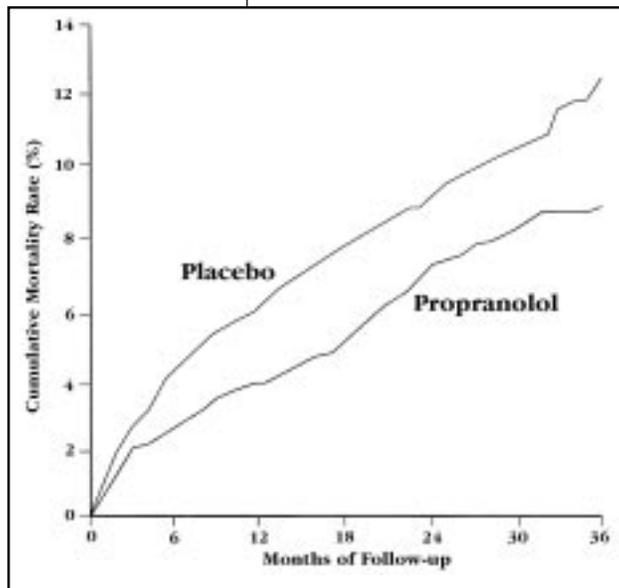
and 35% at two years in survivors of sudden cardiac death who had ejection fraction <30%.[17]

Nonsustained ventricular tachycardia or frequent ventricular premature depolarizations in combination with reduced left ventricular ejection fraction (ie, ejection fraction <40%) identifies patients who are at high risk for sudden cardiac death.[34-37] However, despite this finding, investigators in the Cardiac Arrhythmia Suppression Trial (CAST and CAST-II)[38-40] found that suppression of ventricular ectopy with potent sodium ion channel blocking agents not only failed to reduce mortality but instead increased mortality rates in the population studied, possibly as a result of an ischemia-related proarrhythmic mechanism.[41]

Other predictors of sudden cardiac death include abnormal variability in heart rate,[42-44] abnormal baroreceptor sensitivity,[43,45,46] and abnormal signal-averaged electrocardiogram results.[43,47] However, the lack of high predictive accuracy of these tests (even when they are used in combination) renders them unsuitable for use as a guide to identify patients who should receive aggressive, expensive preventive therapy (with an ICD, for example).

Evaluation of Patients Who Survive Cardiac Arrest

The main issue to be addressed regarding survival of sudden cardiac death is whether the patient has secondary ventricular fibrillation (ie, the cardiac arrest has a reliably identifiable cause) or primary ventricular fibrillation (ie, the cardiac arrest has no specifically identifiable precipitant).

In the rare instance when a reliably identifiable cause can be established, elimination of that inciting influence may be all that is necessary to treat the patient and prevent further cardiac arrest episodes. For example, an episode of torsade de pointes leading to ventricular fibrillation may be clearly related to acute QT prolongation secondary to administration of quinidine or procainamide for treatment of atrial fibrillation. In such a case, especially if the patient has normal left ventricular function, the only required treatment would probably be discontinuation of the drug.

The most common identifiable cause of ventricular fibrillation is acute myocardial ischemia with infarction. For patients who experience cardiac arrest in the presence of new transmural myocardial infarction, the annual risk of having a subsequent cardiac arrest is low (<2%).[22] Therefore, these patients usually require no specific treatment for arrhythmia; instead, further diagnostic evaluation and treatment should be directed at the underlying coronary artery disease.

A cardiac arrest caused by myocardial ischemia resulting from fixed coronary artery disease or coronary artery spasm is most reliably diagnosed in patients who have a history of either angina or documented ST change (elevation or depression). All patients who have ventricular fibrillation should receive coronary arteriography and left ventricular angiography to detect presence of coronary artery disease (or coronary anomalies) and to assess left ventricular function. If the patient has coronary artery disease, the clinician should con-

sider using a functional test (eg, exercise-thallium study or stress echocardiography test) to establish whether the coronary artery disease is physiologically significant. The finding of high-grade, physiologically significant proximal coronary artery disease involving at least one major vessel (especially in the presence of normal left ventricular function) strongly suggests that the cardiac arrest resulted from ischemia and that treatment should therefore be directed solely at revascularization without treating the arrhythmia directly.

Other identifiable reversible causes of ventricular fibrillation are rare but include recreational drug use, severe electrolyte or acid-base disturbance (manifesting as hypokalemia with serum potassium ion level ≤ 3.0 mEq/L, especially in the presence of toxic or near-toxic levels of digoxin) or proarrhythmia resulting from use of antiarrhythmic drugs (Table 1). In general, however, cardiac arrest should be attributed to these factors only if myocardial ischemia and infarction are absent and ventricular function is entirely normal. Even focal or mild left ventricular abnormalities may cause cardiac arrest; therefore, use of an ICD to treat primary arrhythmia may be necessary in these patients, even though some secondary factors may have contributed to the cardiac arrest. Excluding long-QT syndromes (congenital or acquired) and the Brugada syndrome from the differential diagnosis is also important. Patients who survive an episode of torsade de pointes caused by congenital or acquired long-QT syndrome may require substantially different

treatment than do patients with an old myocardial infarct scar. This treatment may range from simply withdrawing use of an offending pharmaceutical agent to implantation of an ICD.

Other diagnostic studies that are often useful in particular instances include standard transthoracic or transesophageal echocardiography, especially as used to assess valvular heart disease or to evaluate patients for presence of right ventricular dysplasia. However, definitive diagnosis in patients with suspected right ventricular dysplasia may require magnetic resonance imaging, right ventricular angiography, or endomyocardial biopsy. Diagnosis of infiltrative disorders (eg, sarcoidosis, amyloidosis, hemochromatosis, or myocarditis) usually requires right ventricular endomyocardial biopsy.

If this assessment of reversible or otherwise treatable causes fails to identify any such factors, the arrhythmic substrate should next be evaluated, usually by an electrophysiologic study. Noninvasive testing (eg, outpatient ambulatory electrocardiographic monitoring, signal-averaged electrocardiography, T-wave alternans, or assessment of variability in heart rate) are of little or no value in evaluating patients whose risk of sudden cardiac death has already been established by actual cardiac arrest. Nonetheless, an electrophysiologic study is often (if not always) done in these patients, even though it may have limited usefulness. The purpose of electrophysiologic study is not to prove that ventricular fibrillation is inducible; inducibility of ventricular fibrillation by pro-

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Patients in whom cardiac arrest is clearly caused by ischemia or infarct may require only a revascularization procedure.

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grammed electrical stimulation is a nonspecific finding regardless of left ventricular function. Instead, the goal of an electrophysiologic study is to evaluate the arrhythmic substrate and to determine how this assessment may impact therapy (even though the patient is likely to receive an ICD). For example, electrophysiologic study often can indicate whether the cardiac arrest may have a treatable precipitating arrhythmic cause (eg, bundle branch reentrant ventricular tachycardia or, especially in young people, Wolff-Parkinson-White syndrome).[48] In these cases, catheter ablation therapy may be the primary (and possibly the only) treatment required. In addition, an electrophysiologic study can establish whether monomorphic ventricular tachycardia can be induced and whether overdrive ventricular pacing can terminate it. These findings are useful when deciding whether to program the ICD to deliver antitachycardia pacing therapy for clinical monomorphic ventricular tachycardia. The finding of easily inducible monomorphic ventricular tachycardia may also indicate that the patient requires adjuvant antiarrhythmic drug therapy to avoid delivery of frequent ICD therapy. An electrophysiologic study requires minimal time and cost and is generally done immediately before implantation of the ICD without removing the patient from the procedure table in the electrophysiology laboratory. Consequently, electrophysiologic testing does not prolong the patient's hospital stay.

Before ICD systems were developed and became widespread, the best available treatment for survivors of sudden arrhythmic death was revascularization (if indicated) and treatment with antiarrhythmic drugs. Upon development, validation, and standardization of programmed electrical stimulation as a reliable and reproducible means to induce monomorphic ventricular tachycardia in patients having the requisite substrate, this technique had become widely used to evaluate and guide the administration of antiarrhythmic drugs in these patients. Patients who had inducible ventricular tachycardia that was suppressed by antiarrhythmic drugs had improved survival compared with patients who had inducible ventricular tachycardia that was not suppressed by drugs. In patients who have experienced cardiac arrest, problems prevent this technique from being widely used today, especially given the success of the ICD in rescuing patients from sudden arrhythmic death. These problems include the relatively low inducibility of the clinical ventricular arrhythmia; lack of reliability, reproducibility, and significance of any induced arrhythmia; and questionable value and reliability of antiarrhythmic drug suppression in this high-risk patient population. In a patient who has suffered cardiac arrest, the clinical significance of inducing monomorphic ventricular tachycardia is unclear at best and possibly totally irrelevant, especially since monomorphic ventricular tachycardia appears only rarely to trigger cardiac arrest.

Treating Survivors of Sudden Arrhythmic Death: Secondary Prevention

Consensus has formed around several treatment principles applicable for certain broad groups of patients. However, in practice, clinicians should approach treatment of each patient individually and recognize that the standard of care can change over time.

Surgical Revascularization

As mentioned above, patients in whom cardiac arrest is clearly caused by ischemia or infarct may require only a revascularization procedure (eg, coronary artery bypass, angioplasty, coronary stenting) as treatment—particularly if the patient's collapse occurred during exercise, was preceded by angina, and is found associated with physiologically significant high-grade proximal coronary artery disease with normal ventricular function. Patients with this clinical profile have done well when treated with coronary revascularization and β-adrenergic blockers.[49,50] Even if the cardiac arrest did not occur during exercise and left ventricular function is not absolutely normal, coronary revascularization therapy alone does appear to provide clinically significant protection to survivors of cardiac arrest: Survival rate for surgically treated patients is 92% at one-year follow-up and 82% at five-year follow-up, whereas patients treated with medical therapy have a survival rate of 80% at one year and 51% at five years.[51-53]

Antiarrhythmic Drug Therapy

Ever since publication of the results of the Cardiac Arrhythmia Suppression Trial (CAST),[38] use of antiarrhythmic drugs as sole treatment for ventricular tachyarrhythmia has become increasingly unpopular. However, the CAST[38] and CAST-II[40] were not designed to address the use of these agents for treating survivors of sudden cardiac death. Rather, CAST and CAST-II were designed to assess the effect of antiarrhythmic agents (administered randomly without

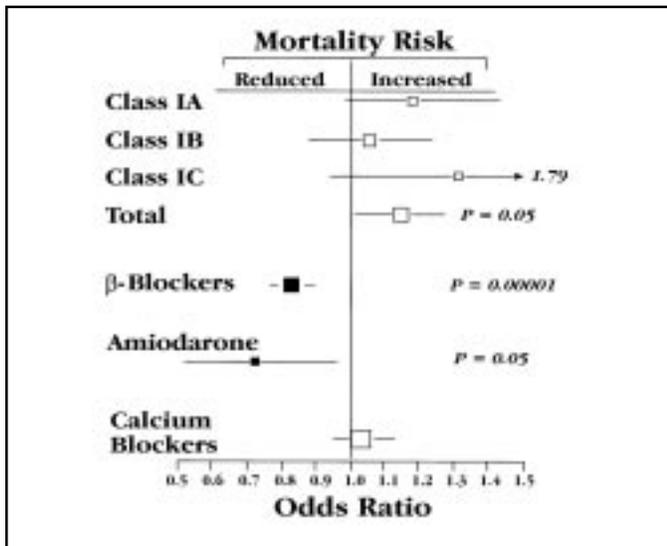**Figure 2. Meta-analysis showing mortality risk associated with antiarrhythmic drugs**

Figure 2. Meta-analysis showing mortality risk associated with antiarrhythmic drugs, presumably secondary to proarrhythmic effects exerted by these agents. Only β-adrenergic blockers and amiodarone appear to reduce risk. Bars indicate 95% confidence intervals; areas of squares are proportional to variance for each drug trial or group of trials.

(Adapted and reproduced with the permission of the publisher and author from: Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized control led trials. JAMA 1993 Oct 6;270(13):1589-95, Figure 1.)[58]
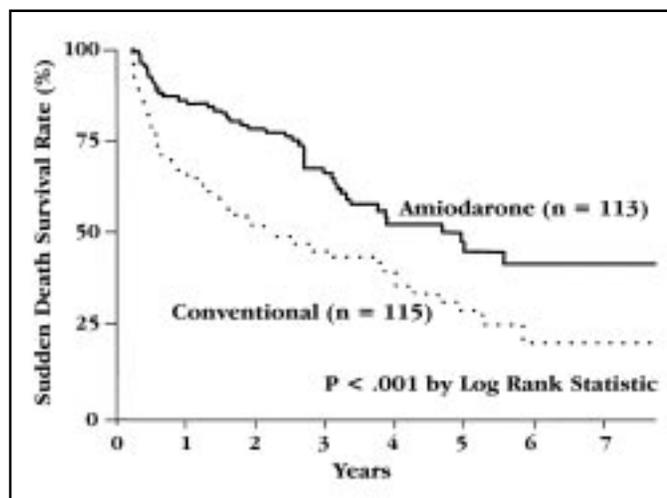

Figure 3. Sudden cardiac death survival rate in the CASCADE study. Survivors of out-of-hospital cardiac arrest were randomized to empirical amiodarone or electrophysiology- or Holter-guided therapy using conventional antiarrhythmic drugs. Endpoints were cardiac arrest from ventricular fibrillation or syncope followed by ICD shock.

(Adapted and reproduced with the permission of the publishers and author from: Randomized antiarrhymthmic drug therapy in survivors of cardiac arrest (the CASCADE Study). The CASCADE Investigators. Am J Cardiol 1993 Aug 1;72(3):280-7, Figure 3.)[59]

electrophysiologic guidance) on survival rates in patients believed to be at high risk for sudden cardiac death because of their previous myocardial infarction and baseline ventricular ectopy. However, prospective and retrospective studies[54-57] have supported the conclusion that empirical use of class IA, IB, and IC antiarrhythmic drugs does not protect against sudden cardiac death. In fact, in patients who have ventricular tachyarrhythmias, these agents may increase mortality rates by a variety of mechanisms, including negative intropism, increasing incidence of ventricular fibrillation during ischemia, proarrhythmia, or decreased variability in heart rate.[54-57] Meta-analysis suggests that β-adrenergic blockers and amiodarone are the only drugs that reduce mortality rates in patients who have had myocardial infarction (Figure 2).[58] Taken together, these data argue strongly against routine empirical use of "conventional" (class I) antiarrhythmic drugs for primary prevention of cardiac arrest in patients who are at high risk for sudden cardiac death and against use of these agents for electrophysiologically guided suppression of inducible ventricular tachyarrhythmia in patients who have had (or who are at high risk for) ventricular arrhythmia or sudden arrhythmic death.

Two class III antiarrhythmic agents—amiodarone and sotalol—provide the greatest hope for achieving safe, effective primary and secondary prevention of cardiac arrest. In survivors of out-of-hospital cardiac arrest, total cardiac mortality and sudden cardiac death are reduced

more effectively by amiodarone than by Holter-guided or electrophysiologically guided antiarrhythmic drug therapy that uses conventional (ie, class I) antiarrhythmic drugs (Figure 3).[59-61] Unfortunately, in patients receiving amiodarone therapy, rates of recurrent sudden cardiac death (assessed by documented ventricular fibrillation or syncope with ICD shock) continue to range from 4.5% to 31% at two-year follow-up.[59,61-64] A class III drug with β-adrenergic blocking effects (d,l-sotalol) has gained some favor, especially after the ESVEM (Electrophysiologic Study Versus Electrocardiographic Monitoring) trial reported that d,l-sotalol reduced recurrence rates for arrhythmia and overall mortality clinically significantly more than conventional antiarrhythmic drugs.[65,66] However, only about 20% of ESVEM patients were survivors of sudden cardiac death, and rates of arrhythmia recurrence with d,l-sotalol remained 21% at one-year follow-up and >40% at four-year follow-up.[65,66] In addition, results of the recent SWORD (Survival With Oral d-Sotalol) Trial[67,68] suggest that the survival benefit is likely to be conferred by the β-adrenergic blocking activity present in racemic sotalol. Among patients at high risk for sudden cardiac death, mortality rates are increased by d-sotalol, which lacks the β-adrenergic blocking effects of d,l-sotalol.[67,68]

Surgical Ablation of Ventricular Tachycardia

Data from 483 patients who had map-directed surgery to eliminate ventricular tachycardia (including many patients who had concomitant coronary artery

bypass surgery) have been reviewed.[69,70] The major problem with this treatment option is the high operative mortality rate (6% to 21%), even in surgical centers with high patient volume. The low operative mortality of ICD implantation (<1%), high success rate for these devices in rescuing victims of ventricular fibrillation, and excellent long-term all-cause survival rate (75% at 36-month follow-up) in patients receiving ICDs has all but eliminated surgery for ventricular tachycardia as a major clinical treatment for sudden cardiac death.

Catheter Ablation

Patients with severe heart disease and inducible monomorphic ventricular tachycardia may not be adequately protected from sudden cardiac death by ablation of a single target form (or multiple target forms) of ventricular tachycardia, even though successful ablation may be possible 60% to 70% of the time.[71,72] This finding is of concern particularly because only a minority of patients who have acutely successful ablation remain free of recurrent ventricular tachycardia. In addition, as mentioned earlier in this discussion, monomorphic ventricular tachycardia is rarely the provoking arrhythmia in victims of sudden cardiac death. Catheter ablation appears to have a role in treating survivors of sudden cardiac death only among patients with bundle branch reentrant ventricular tachycardia[73] and among patients with right ventricular tachycardia resulting from right ventricular dysplasia.[74] Even in these cases—and possibly on the basis of inducibility of other forms of ventricular tachycardia or severity of left ventricular dysfunction—the electrophysiologist must judge whether catheter ablation alone provides adequate protection for these patients; additional therapy with an ICD may be indicated.

Use of Implantable Cardioverter-Defibrillator

The basic ICD system (Table 2) consists of a pulse generator and a transvenous ventricular lead that incorporates sensing and pacing electrodes as well as high-energy defibrillation electrodes (Figure 4). The first ICDs (implanted in the early 1980s) weighed >290 g and had volume >160 cm³. Almost exclusively, those early devices required implantation in a subcutaneous or subrectus abdominal pocket. As with pacemakers, ICD size has decreased dramatically: Devices available today have volume <40 cm³. The small size of these devices allows routine implantation within a subcutaneous pocket in the pectoral region. The lead is inserted transvenously using the axillary, cephalic, or subclavian veins. Modern ICDs are extremely effective at terminating ventricular fibrillation within only a few seconds after onset (Figure 5). In addition to being smaller, ICD devices are incorporating an ever-
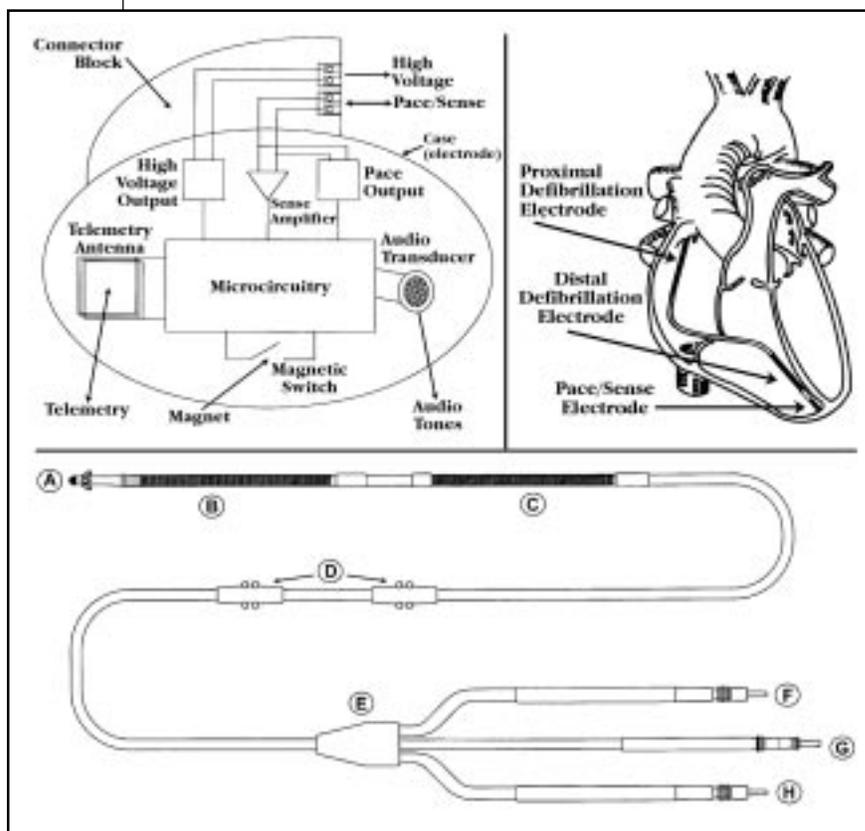

Figure 4. Components of implantable cardioverter-defibrillator systems. Left upper panel: schematic diagram summarizes major components and interfaces of ICD pulse generator. Lower panel: schematic diagram shows typical tripolar transvenous defibrillation lead. A-distal steroid-eluting pace/sense electrode (cathode); B-proximal pace/sense spring electrode (anode) and distal defibrillating spring electrode; C-proximal defibrillating spring electrode; D-anchoring sleeves; E-yoke; F-distal defibrillating electrode terminal (cathode); G-proximal and distal pace/sense electrode terminal; H-proximal defibrillating electrode terminal (anode). Upper right panel: schematic diagram depicts typical position of pace/sense/defibrillation lead in right side of heart.

increasing array of features, including dual-chamber (atrial and ventricular) pacing; rate-responsive pacing; biventricular pacing for patients with clinically significant congestive heart failure and left bundle branch block; and even dual-chamber (atrial and ventricular) defibrillation capabilities for patients with atrial fibrillation and ventricular tachyarrhythmia. Most patients do not benefit from the increased capabilities of these devices, however, and the added cost of these systems should be considered when deciding on the best ICD for each patient.

Since the late 1980s, a number of studies[75-82] have shown that ICDs are the most effective treatment for reducing rates of sudden cardiac death caused by ventricular fibrillation. In a series of 270 patients who received an ICD, the rate of surviving sudden cardiac death was 99% at one-year follow-up and was 96% at five-year follow-up; the total survival rate (sudden and nonsudden) was 92% at one-year follow-up and 74% at five-year follow-up.[75] The largest retrospective series of cardiac arrest survivors[76] observed 331 patients who had received either electrophysiologically guided antiarrhythmic drug therapy or an ICD. This study showed that the total mortality rate was 29% in the 150 patients who received an ICD, whereas total mortality rate was 62% in the 181 patients who did not receive an ICD (Figure 6).[76] The effect was most striking in patients with ejection fraction <40%. This study[76] also showed that left ventricular function was more important in predicting long-term survival rates than was presence of an ICD, because patients with high left

Table 2. Basic functional components of implantable cardioverter-defibrillator systems
Pulse Generator • High-energy defibrillation • Low-energy cardioversion • Antitachycardia pacing • Antibradycardia pacing • Event recording and storage (eg, tachycardia and bradyarrhythmia episodes, shocks/therapies, stored and real-time electrograms
Leads • Atrial sensing/pacing lead (dual-chamber system) • Ventricular sensing/pacing/defibrillation lead (single- or dual-chamber system)
External programming system

Since the late 1980s, a number of studies have shown that ICDs are the most effective treatment for reducing rates of sudden cardiac death caused by ventricular fibrillation.
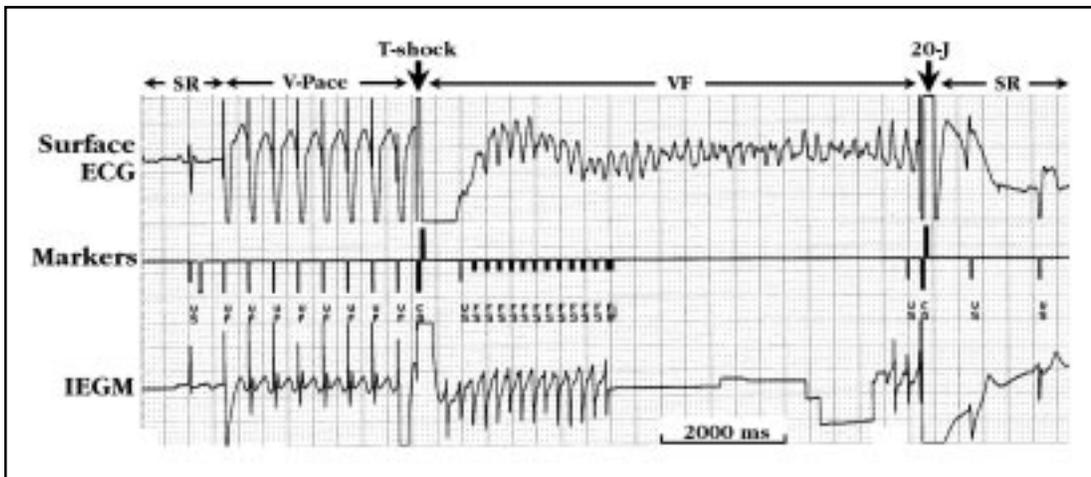

Figure 5. Recording of successfully functioning ICD system illustrates defibrillation testing during device implantation using the shock on T-wave protocol. Shown from top to bottom are a surface ECG recording, "markers" indicating the functions performed by the ICD device, or intracardiac signals being detected from moment to moment, and recorded intracardiac electrograms (IEGM). While the heart is in sinus rhythm (SR), eight pacing stimuli are delivered at a cycle length of 400-msec (V-Pace), after which a low-energy shock (1.2-J) is delivered during the T wave (T-shock). The T-shock induces ventricular fibrillation (VF) that is promptly detected and terminated by a 20-J shock, restoring SR. CD = shock (charge) delivered; FD = ventricular fibrillation detected; FS = ventricular fibrillation sense; VP = ventricular pace; VS = ventricular sense.

ventricular ejection fraction (>40%) and no ICD device had better survival rates than did patients who received an ICD and had low left ventricular ejection fraction (<40%) (Figure 6).[76]

Although ICDs are clearly effective at reducing rates of sudden cardiac death resulting from ventricular fibrillation, a debate has evolved as to whether amiodarone is as effective as ICDs in reducing total mortality rates. Because almost all patients with ventricular tachyarrhythmia or a history of sudden arrhythmic death are elderly, have other chronic diseases, and have poor left ventricular function, these patients have a relatively high total (sudden, cardiac, and noncardiac) mortality rate. According to this argument, even if ICDs reduce the rate of sudden death, these patients nonetheless die from other diseases—or because of poor left ventricular function, these patients die an early cardiac death due to "pump failure." Are ICDs simply an expensive means to change the mode but not the rate of death in these patients? Unfortunately, until recently, the best study[83] on this matter was a retrospective study in which patients receiving an ICD had better overall survival rates than did patients who received amiodarone therapy. The AVID (Antiarrhythmics Versus Implantable Defibrillators) trial is the first prospective study to address this question.[84] The results of that multicenter study (which included survivors of cardiac arrest as well as patients who had a sustained or symptomatic episode of ventricular tachycardia) suggest that treatment with ICDs substantially reduces sudden and total mortality in these patients as compared with empirical amiodarone
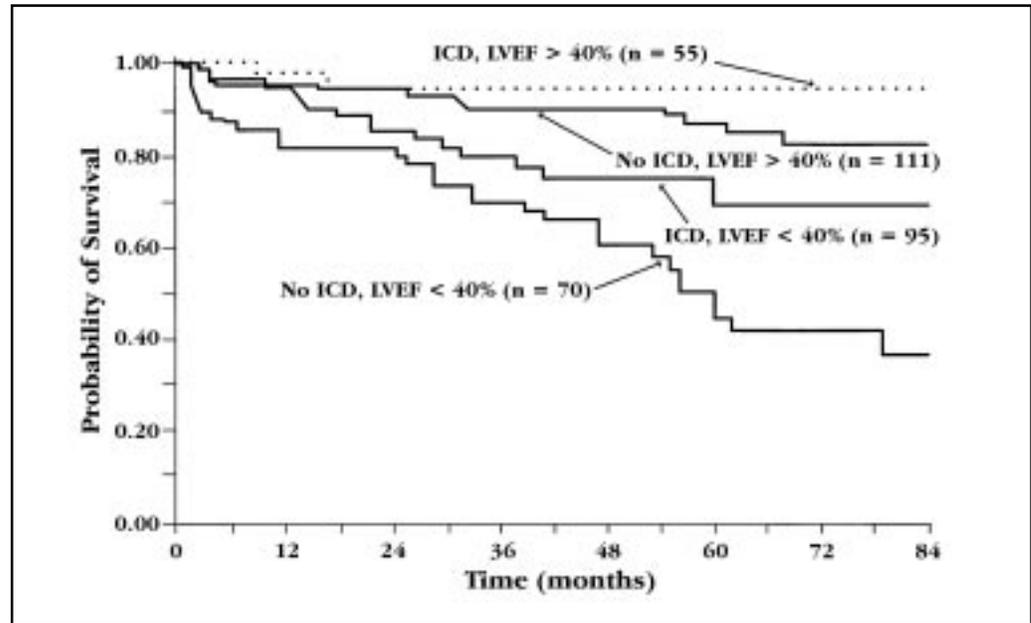

Figure 6. Graph shows survival curves as a function of left ventricular ejection fraction in 331 patients (studied retrospectively) who had out-of-hospital cardiac arrest and were treated with an ICD.
(Adapted and reproduced with the permission of the publisher and author from: Powell AC, Fuchs T, Finkelstein DM, et al. Influence of implantable cadioverter-fibrillators on the long-term prognosis of survivors of out-of-hospital cardiac arrest. Circulation 1993 Sep;88(3):1083-92, Figure 1.)[76]
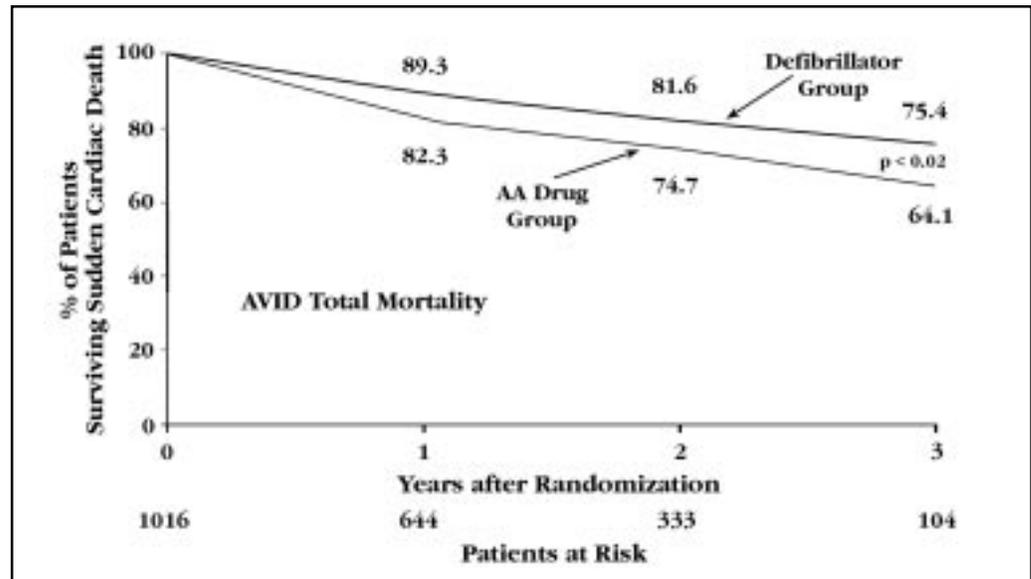

Figure 7. Total mortality curve from the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial, which was terminated prematurely when data indicated that improvement of total survival was clinically significant in patients who received an ICD when compared with those who received either amiodarone or electrophysiologically guided sotalol. AA = antiarrhythmic drug (amiodarone or sotalol) group.
(Adapted and reproduced with the permission of the publisher and author from: A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmic Versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 1997 Nov 27;337(22):1576-83, Figure 1.)[84]

therapy or electrophysiologically guided treatment using racemic sotalol (Figure 7).[84] From one perspective, implantation of ICDs is associated with a 39% decline in overall mortality rate at one-year follow-up as compared with amiodarone therapy; at two-year follow-up, mortality rate is 27%; at three-year follow-up, the rate is 31%.[84] Viewed another way, however, patients who received an ICD had only 2.1 months longer mean survival than did patients who received amiodarone therapy.[84] Although some patients clearly benefit greatly after receiving an ICD, other patients do not benefit at all compared with their counterparts who receive amiodarone therapy. The AVID trial was terminated prematurely after release of the follow-up data showing the statistically significant survival benefit of ICDs compared with amiodarone. As with AVID, survivors of sudden cardiac death and patients with symptomatic sustained ventricular tachycardia enrolled in the Canadian Implantable Defibrillator Study (CIDS)[85] were randomized to receive either amiodarone or an ICD. Although the CIDS data showed improved overall survival for the ICD patients compared with patients who received amiodarone, the difference did not reach statistical significance—unlike the findings of the AVID trial.[85]

Adjunctive Therapy

For decades, β-adrenergic blockers have been shown to reduce total mortality rates and sudden-death mortality rates after myocardial infarction.[29-31,86,87] More recently, in patients with congestive heart failure, carvedilol has been shown to reduce risk of death from 7.8% (in untreated patients) to 3.2% (in treated patients).[88] Although some debate remains, the consensus of most investigators is that angiotensin-converting enzyme (ACE) inhibitors effectively decrease total mortality rates by 18% to 27% in patients who have diminished left ventricular ejection fraction and heart failure.[89,90]

Primary Prevention of Sudden Cardiac Death

The widespread, successful use of ICDs in survivors of cardiac arrest has largely provided secondary prevention for patients who do not have a treatable or reversible cause for that cardiac arrest. However, the tasks of reliably identifying patients at highest risk for a first episode of cardiac arrest and providing cost-effective primary prevention for these patients remains difficult. These tasks are further complicated by the difficulty of reaching consensus on the definition of "high risk." "High risk" is a relative term; some clinicians may apply the term to any patient who has had an acute myocardial infarction or who has abnormal left ventricular function. Screening all such patients by using electrophysiologic testing or empirically treating them with ICDs will
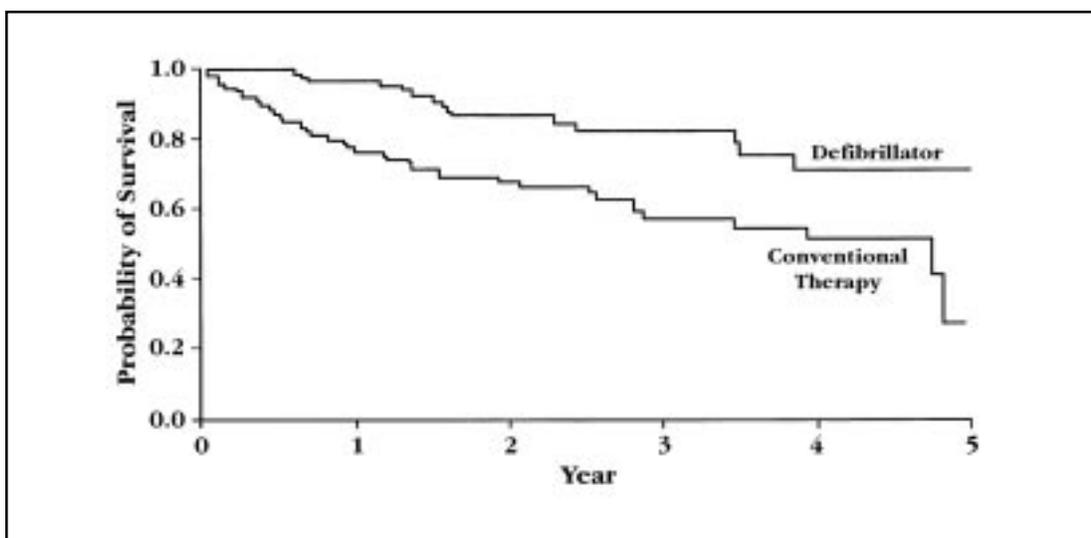
Figure 8. Graph shows survival curves for patients enrolled in MADIT (Multicenter Automatic Defibrillator Implantation Trial). (Adapted and reproduced with the permission of the publishers and author from: Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996 Dec 26;335(26):1933-40, Figure 2.)[92]

Use of β-adrenergic blocking agents is universally considered an important aspect of preventive therapy in patients at high risk for cardiac arrest.

have a substantial economic impact on even the wealthiest society, especially as its proportion of elderly members increases.

Notwithstanding the difficulty of defining "high risk" in this context, use of β-adrenergic blocking agents is universally considered an important aspect of preventive therapy in patients at high risk for cardiac arrest. Compelling data support the effectiveness of these agents in preventive therapy: Even part-time or occasional use of these agents is associated with a clinically significant reduction in total mortality in these patients. This effectiveness of β-adrenergic blockers strongly suggests that sympathetic tone (or balance of sympathetic and parasympathetic tone) may have a crucial role in precipitating sudden cardiac death.

A meta-analysis[91] has shown the value of using electrophysiologic testing to identify patients at high risk for sudden arrhythmic death. Sustained ventricular tachycardia can be induced in 45% of patients with left ventricular dysfunction and nonsustained ventricular tachycardia.[91] During a 20-month follow-up period, 18% of patients with induced tachycardia and 7% of patients without induced tachycardia had an arrhythmic event, regardless of type of antiarrhythmic drug therapy received.[91] The calculated positive predictive accuracy of electrophysiologic testing is 18%, whereas the negative predictive value of this testing is 93%.[91] Thus, electrophysiologic study can more reliably identify patients at low risk for sudden cardiac death than patients at high risk for this condition. Two multicenter randomized con-

trolled trials, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) (Figure 8)[92] and the Multicenter Unsustained Tachycardia Trial (MUSTT) (Figure 9),[93] used electrophysiologic testing for risk stratification in patients who had clinically significant left ventricular dysfunction after myocardial infarction. The MADIT suggested that patients at high risk (ie, patients with poor left ventricular function, nonsustained ventricular tachycardia, and induced sustained ventricular tachycardia not suppressed by intravenous procainamide) have better clinical outcomes after receiving an ICD than after receiving "conventional medical therapy."[92:abstract] The MUSTT study[93] showed that patients who received electrophysiologically guided antiarrhythmic treatment had lower rates of sudden cardiac death than did patients who received no treatment: Rates were 12% versus 18% at two-year follow-up and 25% versus 32% at five-year follow-up. However, the improved survival rates seen for patients who received electrophysiologically guided therapy occurred only in patients who received an ICD. Survival rates for patients with induced tachycardia did not differ according to whether patients were treated exclusively with antiarrhythmic drugs or received no antiarrhythmic drugs. The MUSTT study[93] showed that electrophysiologically guided antiarrhythmic drug therapy has no value for patients with inducible sustained ventricular tachycardia. Instead, the study suggests that placement of an ICD is the only effective antiarrhythmic therapy for primary prevention of sudden cardiac death in patients with inducible sustained monomorphic ventricular tachycardia.[93]
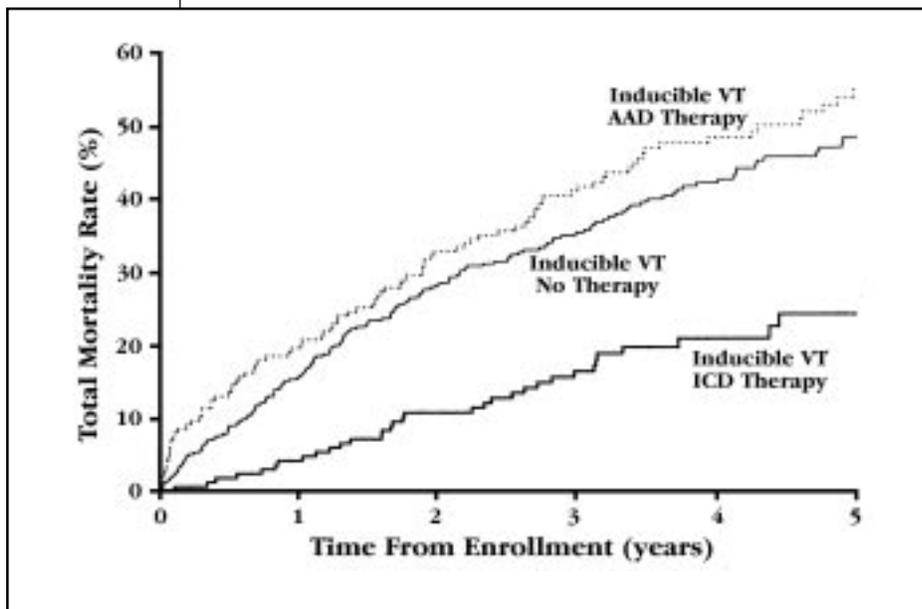
Figure 9. Graph shows survival curves for patients enrolled in MUSTT (Multicenter Unsustained Tachycardia Trial). Survival rate was statistically improved (p < 0.001) in ICD patients compared with untreated patients or with patients receiving electrophysiologically guided drug therapy. AAD = antiarrhythmic drug; ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.
(Adapted and reproduced with the permission of the publisher and author from: Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999 Dec 16;341(25):1882-90, Figure 4.)[93]

Basic Evaluation
History, physical examination, laboratory studies (eg, rule out myocardial infarction, check electrolytes), electrocardiogram, coronary angiography, left ventricular angiogram ± echocardiogram

Patient with ventricular fibrillation cardiac arrest

Reversible Cause Identified?
(eg, ischemia, drug-induced, severe electrolyte disorder)

Yes

Treat Underlying Cause
(eg, ischemia ⟶ revascularization)

No

EP testing
Ventricular tachycardia (monomorphic or bundle branch reentrant)? Noninducible?

Normal left ventricular function?

No

Consider electrophysiologic testing, ICD implantation

Yes

ICD Implantation
(Results of EP testing do not necessarily determine therapy but help guide programming of ICD and assist in patient management.)
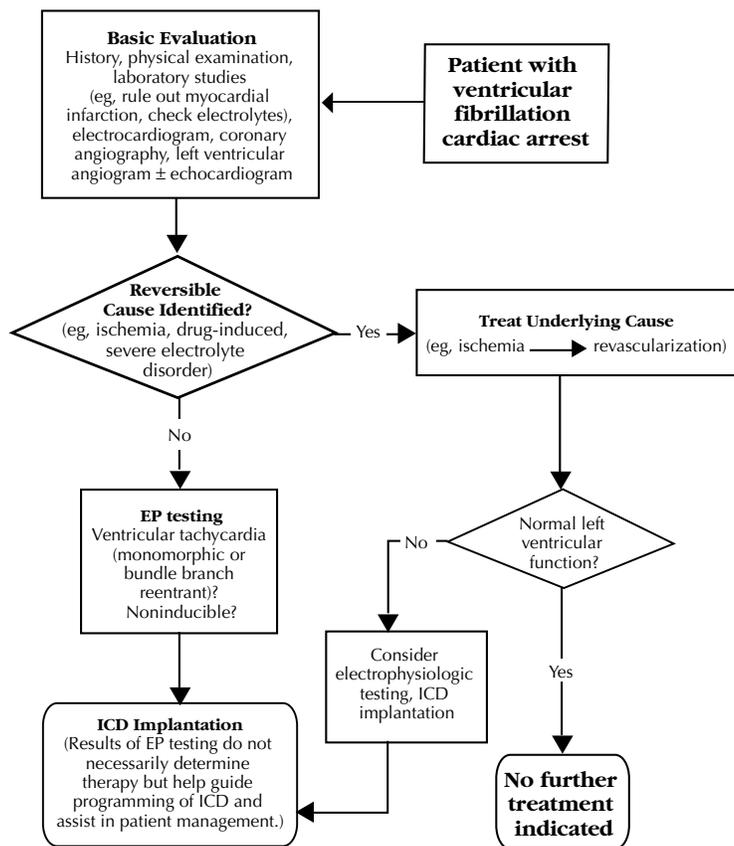
No further treatment indicated

Figure 10. Algorithm summarizes diagnostic and therapeutic clinical management for survivor of ventricular fibrillation cardiac arrest. Unless cardiac arrest is caused by acute myocardial infarction (MI) or is the result of a treatable condition (eg, Wolff-Parkinson-White (WPW) syndrome, ischemia, drug-induced proarrhythmia), recommended therapy is an implantable cardioverter-defibrillator (ICD).

In the recently completed CABG (Coronary Artery Bypass Graft) Patch Trial,[94,95] patients having elective coronary artery bypass surgery who had coronary artery disease, left ventricular dysfunction, and positive results of signal-averaged electrocardiography were randomized to receive an ICD as preventive therapy for cardiac arrest. Unlike the MADIT, the CABG Patch Trial showed that implantation of an ICD did not confer a survival benefit to this high-risk group of patients compared with the control group who received bypass surgery but no defibrillator. Unlike the MADIT patients, enrollees in the CABG Patch Trial were not screened with an electrophysiologic study.

Important multicenter studies currently underway include MADIT-II and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial).[86,96-98] SCD-HeFT is designed to determine whether amiodarone or the ICD can decrease overall mortality rates in patients with coronary artery disease or nonischemic cardiomyopathy who have heart failure (New York Heart Association class II or III) and have left ventricular ejection fraction <35%. The primary endpoint in SCD-HeFT is total mortality; secondary endpoints include a comparison of arrhythmic and nonarrhythmic mor-

tality and morbidity as well as of quality of life, cost-effectiveness of treatment, and incidence of ventricular tachyarrhythmic episodes. MADIT-II proposes to test the hypothesis that ICDs increase survival rates in patients who have a history of previous myocardial infarction and ejection fraction <30%.[96] Candidates for this study have not had cardiac arrest or a symptomatic episode of nonsustained ventricular tachycardia, and they need not even have had asymptomatic nonsustained ventricular tachycardia. MADIT-II participants will not be screened with electrophysiologic testing; instead, they will be randomized either to receive an ICD or not to receive an ICD. The endpoint is total mortality.[96] The MADIT-II study may have a significant effect on use of ICDs if the study shows that these devices are associated with a decline in total mortality rates among the study patients. If empirically based ICD implantation becomes viewed as the standard of care in patients with ejection fraction <30% who have had myocardial infarction, the economic costs to society will be substantial, especially as the population ages.

Current Clinical Management for Survivors of Sudden Cardiac Death

The general treatment algorithm currently used by the Northern California Regional Cardiac Electrophysiology Service of the Kaiser Permanente Medical Care Program is summarized in Figure 10. In general, patients who have had ventricular fibrillation cardiac arrest should be treated with an ICD unless the tachyarrhythmia occurs in the presence of acute myocardial infarction or a reversible cause (eg, clinically significant myocardial

If empirically based ICD implantation becomes viewed as the standard of care in patients with ejection fraction <30% who have had myocardial infarction, the economic costs to society will be substantial, especially as the population ages.

In general, patients who have had ventricular fibrillation cardiac arrest should be treated with an ICD unless the tachyarrhythmia occurs in the presence of acute myocardial infarction or a reversible cause.

ischemia or drug-induced proarrhythmia) can be identified. Although this algorithm provides general management principles, emphasizing that each clinical situation is unique is crucial, and each diagnostic and therapeutic plan must be individualized for each patient. In addition, this treatment algorithm applies to survivors of cardiac arrest and excludes patients who have had an episode of sustained monomorphic ventricular tachycardia, for whom treatment options may include catheter ablation, drug therapy, or ICD implantation, depending on the cause of the monomorphic ventricular tachycardia and on an evaluation of left ventricular function. This algorithm does not address primary prevention in patients at high risk for sudden cardiac death; in this context, definitions for "high risk" and appropriate clinical management for patients so classified is still evolving. A complete discussion of these issues is beyond the scope of the present review. ❖

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A Newer World

"Come, my friends.
'Tis not too late to seek a newer world."

"Ulysses," Alfred, Lord Tennyson, 19th Century poet laureate of England