Clinical Cardiology Frontiers

Predicting and Preventing Sudden Death From Cardiac Causes

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Abstract Sudden cardiac death usually occurs secondary to a ventricular tachyarrhythmia. Even under ideal circumstances only 20% of patients who have an out-of-hospital cardiac arrest survive to hospital discharge. Therefore, aggressive treatment and screening of high-risk patients are mandatory to improve survival rates. Risk stratification of high-risk patients, such as the post–myocardial infarction (MI) population, has been of limited value. Between 70% and 85% of "high-risk" post-MI patients, as defined by these screening tests, will not have a sustained ventricular tachyarrhythmia over several years of follow-up. The use of β-blockers and possibly amiodarone may have some benefit in reducing mortality in high-risk patients after an MI. Several ongoing trials are studying the use of serial drug testing, amiodarone, and implantable cardioverter-defibrillators in reducing the incidence of sudden cardiac death in patients with potentially lethal ventricular arrhythmias. Although implantable cardioverter-defibrillators appear to be superior to antiarrhythmic drugs in reducing sudden cardiac death, total mortality may not be altered. In sustained ventricular tachyarrhythmias, sotalol and amiodarone appear to be superior to other drugs in preventing arrhythmia recurrence. Ongoing trials, such as the Antiarrhythmic Drug versus Implantable Device (AVID) trial may define the best strategy in these high-risk patients. (Circulation. 1994;90:1083-1092.)

Key Words • sudden cardiac death • ventricular tachycardia • ventricular fibrillation • antiarrhythmic drugs • implantable cardioverter-defibrillators

Sudden cardiac death, usually due to a ventricular tachyarrhythmia, accounts for 350,000 to 400,000 deaths annually in the United States and continues to be a major public health problem. Although there is a tendency to focus on sudden cardiac death as a distinct clinical entity, sudden death is more correctly viewed as a ubiquitous final common pathway for a spectrum of cardiac pathologies. Sudden cardiac death has been implicated as a major cause of mortality in every form of heart disease associated with significant regional or global abnormalities of function. In the adult population, coronary artery disease represents the most common cardiac substrate.

Cohort studies of patients who have survived an episode of sudden death have been crucial to understanding this problem. These studies have resulted in the development of a series of strategies that use serial electropharmacological testing, map-guided surgery, and antiarrhythmic devices for treatment of these patients. However, only 1% to 20% of patients experiencing out-of-hospital sudden death survive to hospital discharge.1-3 Thus, aggressive treatment of sudden death survivors cannot significantly affect sudden death mortality.4 The public health aspects of sudden cardiac death can only be addressed by a multifaceted approach that includes prevention of heart disease, widespread cardiopulmonary resuscitation training, identification of the patient at increased risk for sudden death, and intervention to prevent sudden death focused on these high-risk individuals. The primary purpose of this article is to review the major efforts to identify the patient at high risk for sudden arrhythmic death and to highlight both completed and ongoing efforts to prevent manifestation of this clinical entity. The implications of recently completed and ongoing studies concerning patients with clinically manifest sustained arrhythmias are also briefly discussed.

Sudden Death Prediction

Since the risk of sudden cardiac death in the unselected adult population is only 2 per 1000 persons per year, screening of unselected patients is impractical.5 As a result, risk stratification efforts have focused on groups with known heart disease. The most convenient group for risk stratification studies is the post–myocardial infarction (MI) patient population. Techniques reported to be of value in identifying high-risk patients include (1) ambulatory electrocardiographic recordings, (2) measurement of left ventricular function, (3) signal-averaged electrocardiography, (4) assessment of heart rate variability, (5) determination of reflex baroreceptor sensitivity, (6) identification of repolarization alternans, and (7) invasive electrophysiological testing.

Ambulatory Electrocardiography

Observations in coronary care units indicate that sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are often preceded by frequent or complex ventricular ectopy.6,7 Epidemiological observations also indicate that ventricular premature complexes (VPCs) in ambulatory patients are associated with an increased incidence of sudden death.8 Long-term ambulatory recordings increase the sensitivity for detection of asymptomatic arrhythmias and reduce errors due
to variability in the occurrence of VPCs and complex ventricular arrhythmias. However, day-to-day variability as well as long-term variability due to a changing cardiac substrate still must be taken into account when using Holter monitoring techniques.

Kotler et al. reported the prognostic importance of ambulatory electrocardiographic findings in 160 post-MI patients. Twelve of 14 patients experiencing sudden death during follow-up had frequent or complex ectopy. Similar findings were reported by Vismara and colleagues in a smaller series. These early reports formed the basis of a much larger study by Ruberman et al., who applied long-term electrocardiographic recording techniques to the post-MI patient population by recording cardiac rhythm for a full hour in MI survivors. They demonstrated a threefold increase in sudden death among patients with complex ventricular arrhythmias (R on T, bigeminy, runs of two or more VPCs, or multiform VPCs) compared with patients without complex arrhythmias. Conversely, frequent and complex VPCs have little prognostic significance in asymptomatic healthy adults.

Suppression of VPCs in the coronary care unit reduces the subsequent occurrence of VT and VF in the patient with an acute infarction. Reasoning by analogy, it was presumed that VPC suppression, as assessed by Holter, would result in protection from sudden death for the post-MI patient. However, the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that Holter-guided suppression of VPCs with flecainide and encainide resulted in an increased occurrence of sudden death. In CAST II, a trend toward enhanced mortality was noted in patients treated with moricizine. Thus, while the ambulatory electrocardiogram identifies a post-MI patient at increased risk, the usefulness of Holter-guided therapy in this setting remains in doubt. Consequently, we no longer routinely perform Holters in post-MI patients without complications.

Left Ventricular Function

Left ventricular function is the most important determinant of overall survival following infarction. The 1-year cardiac mortality rate for a post-MI patient with a radionuclide ejection fraction greater than 40% is less than 4%; the annual mortality for a patient with an ejection fraction less than 20% is almost 50%. Left ventricular function may also be the single best predictor of the risk for sudden death as well. In a study of 395 patients with coronary disease undergoing catheterization, Califf et al. found a strong correlation between ejection fraction and ventricular arrhythmia score. Ejection fraction but not arrhythmia score affected prognosis independently.

Conversely, multicenter studies of more homogeneous post-MI populations suggest that Holter data and ventricular function are independent predictors of sudden death. Data from the Multicenter Post-Infarction Research Group and the Multicenter Investigation of the Limitation of Infarct Size indicate that the risk of frequent or complex ventricular arrhythmias, as assessed by Holter, is additive to the risk of a low ejection fraction. In more recent studies comparing risk stratification by signal-averaged electrocardiogram and Holter with noninvasive assessment of left ventricular function, ejection fraction remains an important parameter.

Since left ventricular function affects many clinical decisions in patients with coronary disease, we measure ejection fraction routinely in the post-MI patient.

Signal-Averaged Electrocardiogram

Holter use for the prediction of sudden death risk presupposes that nonsustained arrhythmias detected by monitoring are markers for more lethal sustained arrhythmias. In contrast, the signal-averaged electrocardiogram detects evidence of delayed or slowed conduction, the substrate for sustained reentrant ventricular arrhythmias. Studies in patients with sustained arrhythmias confirm a high correlation between arrhythmias inducible by programmed electrical stimulation and the presence of late potentials and low-amplitude (1 to 2 μV), high-frequency signals at the end of the QRS. Kuchar et al. found late potentials to be associated with an increased incidence of sudden death in the post-MI patient population. In multivariate analysis, the information provided by the signal-averaged electrocardiogram added significantly to the information provided by ejection fraction. The combination of an abnormal signal-averaged electrocardiogram and an ejection fraction less than 40% was associated with a 34% incidence of arrhythmic events during a median follow-up of fourteen months. Absence of both a reduced ejection fraction and signal-averaged electrocardiographic abnormality was associated with a favorable prognosis. Gomes et al., similarly found the presence of late potentials to be the most sensitive predictor of arrhythmic events in a prospective study of 115 post-MI patients. Unfortunately, the signal-averaged electrocardiogram is less sensitive in anterior infarctions than in inferior infarctions and a standard way to deal with patients who have baseline QRS abnormalities like bundle branch block has yet to evolve.

Heart Rate Variability

Although Schneider and Costiloe first reported the relationship between sinus arrhythmia and prognosis after myocardial infarction more than 25 years ago, assessment of heart rate variability has only recently become available to the clinician. Heart rate variability can be quantitated in a number of ways and is a useful index of autonomic tone. In a report from the Multicenter Post-Infarction Group, Kleiger et al., demonstrated that decreased heart rate variability is an important indicator of prognosis post-MI. In multivariate analysis, heart rate variability added significant prognostic information to other parameters. A study of 487 post-MI patients by Farrell et al. found that decreased heart rate variability was more predictive of arrhythmic events than the presence of late potentials, Holter derived data, treadmill test results or ejection fraction. In multivariate analysis of combinations of risk factors, the combination of late potentials by signal-averaged electrocardiogram and reduced heart rate variability was more predictive than any other combination.

Baroreceptor Sensitivity

Baroreceptor sensitivity, like heart rate variability, reflects the influence of the parasympathetic nervous system on the heart. Baroreceptor sensitivity is measured as the slope of a regression line relating the beat-to-beat heart rate change in response to a change in blood
pressure. Blood pressure change is typically accomplished by the administration of a small bolus of phenylephrine.\textsuperscript{32} Schwartz et al,\textsuperscript{33} who studied baroreceptor sensitivity in a chronic canine infarction model, report that baroreceptor sensitivity is reduced after infarction. The lowest levels of vagal influence are associated with an increased susceptibility to sudden death in their experimental model.\textsuperscript{33} In a small group of post-MI patients, a reduced 2-year survival was observed in patients with low baroreceptor sensitivity.\textsuperscript{34}

Farrell et al\textsuperscript{35} found that reduced baroreceptor sensitivity was highly predictive of sustained arrhythmia induction at electrophysiological study in a post-MI patient population of 68 patients. Late potentials, ejection fraction, indices of heart rate variability, and exercise tests were less predictive.\textsuperscript{35} The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, a multicenter prospective study of 1200 post-MI patients, should further characterize the value of post-MI baroreceptor sensitivity testing.\textsuperscript{32}

Electrical Alternans Measurement

The latest addition to what has become an extensive array of post-MI risk-stratification tests is the assessment of electrical alternans. Electrical alternans on the surface electrocardiogram has been reported to be a harbinger of sudden death.\textsuperscript{36} Rosenbaum et al\textsuperscript{37} have employed signal-analysis techniques to quantify electrical alternans in a series of patients referred for electrophysiological study. The techniques are sensitive enough to detect alternans not apparent on the standard electrocardiogram. Alternans of the ST segment and T wave, ie, repolarization alternans, correlates with the induction of sustained arrhythmias at electrophysiological study. Furthermore, the absence of repolarization alternans correlates with arrhythmia-free survival.\textsuperscript{38} The pathogenesis of repolarization alternans in patients susceptible to malignant arrhythmias remains to be elucidated. This technique merits further validation in larger scale studies of unselected post-MI patients.

Risk Stratification Using Electrophysiological Studies

If the methods available to prevent ventricular arrhythmias were safe and highly effective, noninvasive risk stratification would suffice. However, the pharmacological agents used in large-scale prevention trials are often ineffective when used empirically and are associated with significant toxicity. These factors have fostered a number of studies having the common goal of further refining risk by invasive electrophysiological study. Many reports have described the use of routine electrophysiological study in the post-MI patient.\textsuperscript{38–46} Most have found the results of electrophysiological study in the patient without complications after MI to be poorly predictive of sudden death. Studies that have indicated a prognostic role have targeted patients in high-risk groups (eg, patients with congestive heart failure or conduction abnormalities).

The use of Holter monitoring to target higher-risk patients for electrophysiological study has also been reported by a number of investigators. In their meta-analysis of 12 series of patients with nonsustained VT, Kowey et al\textsuperscript{47} report that of 926 patients, 818 (88%) had coronary disease and 303 (33%) had inducible sustained arrhythmia. Eighteen percent of inducible patients had arrhythmic events during a mean follow-up of 19.4 months. Only 7% of patients without inducible arrhythmias experienced events during the same follow-up period. Analysis of these findings is confounded by the fact that 83% of patients with inducible arrhythmias received antiarrhythmic agents while only 13% of patients not inducible received antiarrhythmic therapy.\textsuperscript{47} Thus, whether inducibility per se or antiarrhythmic therapy is responsible for the increased number of arrhythmic events cannot be determined. What can be stated is that patients who are not inducible have an excellent prognosis and are unlikely to benefit from treatment.

Risk Stratification in Cardiomyopathy

After validation in the post-MI patient, risk stratification techniques have been applied to patients at risk for lethal arrhythmias from other cardiac disease processes. The severity of left ventricular dysfunction is an important determinant of prognosis in patients with dilated cardiomyopathy.\textsuperscript{48} The presence of arrhythmias on Holter is associated with increased risk for sudden cardiac death in these patients as well as patients with hypertrophic cardiomyopathy.\textsuperscript{49–51} The signal-averaged electrocardiogram is more frequently abnormal in patients with hypertrophic and dilated cardiomyopathies who have sustained ventricular arrhythmias.\textsuperscript{52,53} Mancini et al\textsuperscript{54} prospectively collected signal-averaged electrocardiographic data in patients with dilated cardiomyopathy and found a strong correlation between arrhythmic events and bundle branch block on baseline electrocardiogram or signal-averaged electrocardiographic abnormalities. Heart rate variability, baroreceptor sensitivity, repolarization alternans, and electrophysiological study have not been as extensively studied in nonischemic disease processes.

Sudden Death Prediction: Summary

In aggregate, the noninvasive and invasive risk stratification efforts employed separately or together do a reasonable job of identifying low-risk patients. This group can be spared potentially hazardous therapies. However, most patients remaining in the high-risk groups after risk stratification will never have an arrhythmic event. More specific means to identify the patients at highest risk are still needed.

Sudden Death: Primary Prevention

The routine application of expensive risk-stratification measures can be legitimately questioned unless these efforts are combined with effective risk-reduction strategies. Fortunately, the available evidence indicates that sudden cardiac death can be prevented. Epidemiological data indicate that risk-factor modification and primary prevention of coronary artery disease are largely responsible for the reduction in the incidence of sudden cardiac death during the last four decades.\textsuperscript{55,56} Additionally, several trials focused on sudden death prevention in high-risk patient groups have been completed or are ongoing. The completed studies demonstrate the potential value of several interventions in sudden death prevention.
Pharmacological Intervention: β-Adrenergic Receptor Blockers

Since β-adrenergic receptor blocking agents (β-blockers) have both antiarrhythmic and anti-ischemic properties, the choice of these agents for early use in large-scale post-MI trials is understandable. In a preliminary study, Ahlmark and Saetre reported a statistically significant reduction in sudden death during 2 years of follow-up after MI in patients treated with alprenolol. Many subsequent β-blocker trials have reported reduction in total mortality but were of insufficient size to determine the effect of treatment on sudden death mortality. However, reduction in sudden death by β-blockade has been confirmed by two large studies, a Norwegian multicenter trial employing timolol and the β-Blocker Heart Attack Trial conducted in the United States that used propranolol. The benefit of β-blockade is greatest in those patients at highest risk for sudden death, i.e., patients with poor ventricular function and complex ectopy as assessed by Holter. However, suppression of ectopy is not a requisite for the benefits of β-blockade.

β-Blockade may also be of value in sudden death prevention for patients with dilated cardiomyopathy. Preliminary studies indicate a trend toward improvement in overall survival, although limitations in study size preclude analysis of cause-specific mortality.

Pharmacological Intervention: Angiotensin-Converting Enzyme Inhibitors

The value of vasodilators, hydralazine, and nitrates in combination or angiotensin-converting enzyme inhibitors in the reduction of mortality in patients with symptomatic heart failure or reduced left ventricular function has been well demonstrated. Two Veterans Administration cooperative studies (V-HEFT I and II), the Studies of Left Ventricular Dysfunction (SOLVD) trial, the CONSENSUS I trial conducted in Scandinavia, and the Survival and Ventricular Enlargement (SAVE) trial in post-MI patients in North America are concordant and provide compelling evidence that vasodilators reduce overall mortality as well as mortality due to progressive heart failure. However, the studies that examined cause-specific mortality, i.e., sudden versus nonsudden death, have seemingly disparate results. The SOLVD investigators found no effect of enalapril on sudden cardiac death in patients with reduced (less than 35%) ejection fractions and no prior treatment for congestive heart failure. The CONSENSUS I trial reported a similar finding in severely symptomatic patients (New York Heart Association Class IV congestive failure). In contrast, the V-HEFT II study reported a significant reduction in sudden death when enalapril was used rather than hydralazine and nitrates in symptomatic patients with noninvasive evidence of cardiac dysfunction.

The discrepancies among the vasodilator trials in reported effects on sudden death warrant consideration. The different patient populations studied presumably account for some of the differences. Relatively asymptomatic patients (SOLVD study) appear to have a better prognosis from the standpoint of sudden death than patients with more symptoms and the same degree of ventricular dysfunction. On the other extreme, prognosis in severely ill patients (CONSENSUS I) may be so dependent on the degree of heart failure that sudden death intervention has minimal effect. Only 26% of the deaths in the CONSENSUS I trial were sudden deaths, less than in the other trials. Patients with intermediate symptoms, such as the V-HEFT patients, may be the most likely to benefit from therapy. Apparent differences may also be due to the different definitions of sudden cardiac death used in the various studies.

The mechanism by which angiotensin-converting enzyme inhibitors reduce sudden death remains to be elucidated. The SAVE study suggests that one mechanism may be the reduction in recurrent myocardial infarctions.

Pharmacological Intervention: Antiarrhythmic Drugs

In contrast to the reports of favorable effects of β-blockers and vasodilators, the results of trials using conventional antiarrhythmic agents. Preliminary studies employing antiarrhythmic agents such as phenytoin, aprindine, tocainide, procainamide, mexiletine, and sotalol report no improvement in survival with drug treatment. However, these trials were of insufficient size to make definitive conclusions. These studies led to the inception of the Cardiac Arrhythmia Pilot Study (CAPS) and the CAST I and II trials. The goal of CAST I and II was to determine whether Holter-guided suppression of ventricular arrhythmias with flecainide, encainide, or moricizine provided survival benefit in post-MI patients at moderate risk for sudden death. The finding of increased sudden death among the treatment groups of these studies has been much publicized. The results of CAST I and CAST II cannot be extrapolated to other drugs, other patient groups, or treatment guided by other means. However, the CAST trials underscore the fact that the risks of antiarrhythmic therapy are significant and illuminate the importance of well-designed, controlled clinical trials in assessment of interventions to prevent sudden death.

Amiodarone was excluded from the CAST investigations as well as many earlier controlled trials because of its complicated pharmacokinetics and concern for the incidence of end-organ toxicity. However, the low incidence of significant proarhythmia and the demonstration that most pulmonary toxicity is avoidable at low-dose ranges have resulted in considerable interest in the use of this agent for sudden death prophylaxis. In the Basel Antiarrhythmic Study (BASIS), post-MI patients with complex ventricular ectopy were randomized to empiric low-dose amiodarone (200 mg/d), individualized therapy guided by Holter, or no treatment. Total mortality was less at 1 year of follow-up in the amiodarone group than in the control group. Total mortality differences between the amiodarone group and the Holter-guided therapy group were not significantly different. Due to the relatively small number of patients studied, differences in sudden death mortality were not significantly different between any two of the three groups. In comparison with control subjects, the improved survival of the amiodarone-treated patients has persisted throughout an average follow-up of 6 years. Surprisingly, post hoc subgroup analysis indicates that the
beneficial effects of amiodarone were limited to those patients with ejection fractions greater than 40%.

Ceremuzynski et al. have recently reported a randomized, double-blind, placebo-controlled trial of amiodarone in maintenance doses of 100 to 400 mg/d in post-MI patients. Patients were selected for the study specifically because they had clinical contraindications to \( \beta \)-blockade such as heart failure, asthma, diabetes, or symptomatic peripheral arteriosclerosis. Lack of ventricular function, Holter assessment, or signal-averaged electrocardiographic criteria were used to screen patients for the study. Total mortality as well as cardiac mortality were both significantly reduced in the amiodarone treatment group. There was a 30% occurrence of some adverse reaction to amiodarone therapy. However, most reactions were fairly minor and pulmonary toxicity occurred in only one patient. The results of this study suggest that amiodarone may be useful in the post-MI patient who has a contraindication to \( \beta \)-blockade.

A larger role for amiodarone in the management of patients after MI is under investigation in complementary multicenter trials in Europe and Canada. Patients in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) are selected on the basis of ventricular arrhythmias on Holter recorded soon after infarction. In the European Myocardial Infarction Arrhythmia Trial (EMIAT), patients are selected on the basis of a reduced ejection fraction without regard to arrhythmia status. Both studies use low dose-amiodarone (less than 400 mg/d) and have similar end points, ie, total and cardiovascular mortality. In a small CAMIAT pilot study, a trend toward a reduction in the incidence of arrhythmic death or resuscitated ventricular fibrillation was observed with amiodarone treatment. More importantly, the incidence of amiodarone toxicity was sufficiently low to sanction the larger CAMIAT study. The results of CAMIAT and EMIAT are much anticipated: these two studies should clarify the role of amiodarone in the post-MI patient.

The favorable hemodynamic profile of amiodarone has resulted in interest in its use to prevent sudden death in patients with dilated cardiomyopathy. In uncontrolled series, Cleland et al. report favorable effects of amiodarone in patients with heart failure. A randomized, controlled trial of amiodarone is being conducted by the Veterans Administration in patients with congestive heart failure who are being treated concomitantly with angiotensin-converting enzyme inhibitors or other vasodilators.

Finally, McKenna et al. report that amiodarone therapy reduced the incidence of sudden death in a high-risk group of 53 hypertrophic cardiomyopathy patients. No patient experienced sudden death during 18 months of follow-up. This result was statistically significant compared with historical controls. In contrast, Fananapazir et al. report six deaths among 50 hypertrophic cardiomyopathy patients within 5 months of starting amiodarone. The place of amiodarone in patients with hypertrophic cardiomyopathy can probably be determined only by a concurrently controlled randomized trial.

**Revascularization and/or Reperfusion as Prophylaxis**

Data from the Coronary Artery Surgery Study (CASS) indicate that myocardial revascularization prevents sudden cardiac death in high-risk patient groups. Patients with three-vessel disease and congestive heart failure treated surgically had a 9% incidence of sudden death during a follow-up of 5 years. Similar patients treated medically had a 31% incidence of sudden death. Evidence suggests that acute intervention at the time of acute infarction also has a favorable effect on the subsequent occurrence of life-threatening arrhythmias. Compared with patients with occluded arteries, patients with patent infarct-related arteries have a lower incidence of late potentials on signal-averaged electrocardiogram and a lower incidence of inducible arrhythmias at electrophysiological study. These findings are not entirely due to preservation of ischemic myocardium since late reperfusion by angioplasty still produces benefit. Longer follow-up is required to determine whether the reduction in late potentials and inducible arrhythmias results in a reduced incidence of sudden death.

**Prophylaxis Using Implantable Cardioverter-Defibrillators**

Several ongoing multicenter trials use prophylactic cardioverter-defibrillator therapy in patients at high risk for sudden death. Factors that favor this device include the success of cardioverter-defibrillators in sudden death prevention in large reported series, the low efficacy of many available antiarrhythmics, and the traditional pitfalls of chronic medical therapy, such as compliance, convenience, and toxicity. On the other hand, the expense of device therapy and the surgical complications of implantation mandate the conduct of well-controlled trials before prophylactic use of implantable cardioverter-defibrillators becomes widespread.

Two of the three ongoing multicenter investigations, the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT), target patients with coronary disease who have reduced ejection fractions and nonsustained VT. A prior infarction is required for inclusion in MADIT but not for MUSTT. In MADIT, patients meeting entrance criteria who have inducible arrhythmias at electrophysiological study and who cannot be rendered noninducible by intravenous procarbamide are randomized to cardioverter-defibrillator implantation or conventional therapy. Conventional therapy may include anything from no treatment to electrophysiologically guided drug trials or amiodarone.

In MUSTT, inducible patients are randomized to no therapy or to electrophysiologically guided therapy. The initial agent used is a Class Ia agent, propafenone, or sotalol. In the second round of treatment, these same agents can be used singly or in combination with either mexiteline or acebutolol. All drugs not previously used as well as amiodarone can be used in the third and subsequent rounds. At least two unsuccessful drug trials are required before implantable devices can be employed. The primary end points of MUSTT are arrhythmic death and cardiac arrest. MUSTT should clarify the role of electrophysiologically guided treatment in these relatively high-risk patients while MADIT should be valuable in determining whether the risks and expense of prophylactic device implantation are warranted.

Another multicenter trial, the Coronary Artery Bypass Graft (CABG) Patch Trial, is designed to deter-
mine the role of implantable cardioverter-defibrillator implantation in high-risk patients undergoing surgical revascularization. The rationale for this study comes from CASS registry data reported by Alderman et al.\textsuperscript{97} and a similar retrospective study by Hochberg et al.\textsuperscript{98} The 3-year mortality of patients with reduced (less than 35%) ejection fractions undergoing bypass surgery is approximately 30%. Analysis indicates that arrhythmias cause up to 40% of deaths in the post-CABG patient with poor ventricular function. A pilot study demonstrated a higher postsurgical mortality in patients who had a positive signal-averaged electrocardiogram compared with patients without late potentials. In CABG Patch, patients with ejection fractions less than 36% and late potentials on signal-averaged electrocardiograms are randomized intraoperatively after bypass surgery to implantable cardioverter-defibrillator implantation or no further therapy.\textsuperscript{99} Patients too unstable to undergo device implantation and testing are excluded from the study. Study end point for CABG Patch, as with MA-DIT, is total mortality. CABG Patch should clarify the role of prophylactic device use in very-high-risk patients who have already assumed the risks of bypass surgery.\textsuperscript{99}

**Sudden Death Survivors:**

**Secondary Prevention**

At least 80% of patients who have suffered an out-of-hospital cardiac arrest will not survive to hospital discharge.\textsuperscript{100} Of the survivors, 50% will be dead within 3 years.\textsuperscript{100,101} Thus, aggressive management of cardiac arrest survivors is mandatory for the long-term survival of these patients. Interpretation of trials involving patients with sustained “malignant” ventricular tachyarrhythmias has been difficult due to the nonhomogeneous populations included in many studies. Patients with recurrent well-tolerated VT and VT-related syncope are often lumped with sudden death survivors. Besides the aggressive treatment of reversible causes, treatment approaches have included antiarrhythmic therapy or implantation of a cardioverter-defibrillator.

**Antiarrhythmic Therapy in Survivors of Cardiac Arrest**

Antiarrhythmic approaches in high-risk patients have included empiric antiarrhythmic therapy and Holter-guided and/or electrophysiologically guided antiarrhythmic therapy. In general, empiric use of type I antiarrhythmic agents has been associated with an enhanced mortality instead of improved survival.\textsuperscript{102,103} Empiric use of \(\beta\)-blocking drugs may have a role in reducing mortality as shown by improved survival of patients taking \(\beta\)-blockers in a study by Hallstrom et al.\textsuperscript{103} Preliminary data from the Cardiac Arrest Study Hamburg (CASH) suggest that metoprolol, propafenone, or amiodarone are not as effective as the implantable cardioverter-defibrillator in preventing sudden cardiac death. However, after several years of follow-up total mortality in the metoprolol group was not significantly different from that in the amiodarone or cardioverter-defibrillator groups.\textsuperscript{104}

Empiric amiodarone has been used for years with anecdotal reports of a high efficacy rate. In large reported series, amiodarone efficacy correlates poorly with sustained arrhythmia induction at baseline electro-physiological study or demonstration of arrhythmia suppression on repeat study.\textsuperscript{105,106} Thus, prospective controlled trials of empiric amiodarone use in patients with malignant arrhythmias are warranted. In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) trial,\textsuperscript{107} amiodarone reduced the incidence of sudden cardiac death compared with other antiarrhythmics guided by serial electrophysiological testing. However, sudden death rates were quite high in both groups, causing the investigators to implant cardioverter-defibrillators in over 40% of the study population.

The role of empiric amiodarone will be better defined when the results of two ongoing trials, the Canadian Implantable Defibrillator Study (CIDS)\textsuperscript{108} and the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial\textsuperscript{109} are known.

**Holter versus Electrophysiologically Guided Antiarrhythmic Therapy**

Multiple studies have demonstrated that Holter-guided antiarrhythmic therapy has little benefit in reducing mortality except in those patients with high-density arrhythmias.\textsuperscript{110} In contrast, multiple studies suggest that rendering patients noninducible by electrophysiologically guided therapy improves survival of patients who have experienced a cardiac arrest.\textsuperscript{111-115} However, these studies used historical controls. Partial efficacy, defined as a slowing of inducible VT to a point of hemodynamic stability, also appears to improve survival.\textsuperscript{116,117} Few well-performed studies have compared the noninvasive versus invasive approaches. Mitchell et al.\textsuperscript{118} report that arrhythmia recurrence is more common in Holter-guided than in electrophysiologically guided therapy. However, the results of the Electrophysiology Study Versus Electrocardiographic Monitoring (ESVEM) trial\textsuperscript{119} suggest that after 2 years of follow-up, Holter-guided therapy is as predictive as electrophysiologically guided therapy in determining the recurrence of ventricular tachyarrhythmias. In ESVEM, sotalol was superior to other drugs studied in preventing arrhythmia recurrence.\textsuperscript{120} A full critique of ESVEM is beyond the scope of this review. However, several conclusions can be made. (1) Electrophysiologically and Holter-guided therapy were equally but poorly predictive of drug efficacy; 58% of patients had arrhythmia recurrence at 2 years of follow-up. (2) Results of ESVEM cannot be extrapolated to noninducible patients or patients with infrequent spontaneous arrhythmia. (3) Results of this study also cannot be extrapolated to amiodarone-treated patients. (4) Sudden death rates in ESVEM exceeded those achievable by the use of implantable cardioverter-defibrillators.

**Implantable Cardioverter-Defibrillators to Prevent Recurrences**

In patients with malignant ventricular tachyarrhythmias, the implantable cardioverter-defibrillator has a reported 5-year sudden death rate of 4.4% to 4.5%.\textsuperscript{121,122} Although no controlled trials exist, this marked reduction in sudden death compared with historical controls is quite impressive. However, total 5-year mortality in patients treated with implantable cardioverter-defibrillators is still 26%. Other causes of
death include operative mortality, heart failure deaths, and death from noncardiac causes.

Some investigators have suggested that total mortality should be the primary end point of sudden death prevention trials. In this regard, comparison of implantable devices to drug therapy as a frontline treatment strategy has not been well tested. Results of the CASH trial suggest that the implantable cardioverter-defibrillator is superior to metoprolol or amiodarone in preventing sudden death but not total mortality. Because of these findings, the AVID trial is underway to determine whether the "best drug therapy"—empricamiodarone or electrophysiologically or Holter-guided sotalol—is equivalent, superior, or worse than implantable device treatment in high-risk patients. The primary end point of this study will be total mortality.

Conclusions

The multicenter trials, both completed and ongoing, provide cause for optimism, for it is apparent that sudden cardiac death can be mediated by prophylactic therapy. Individual trials focusing on a relatively homogeneous patient group have been crucial to demonstrating a favorable treatment effect. However, there are a few themes that appear to transcend individual studies and that may, perhaps, be important in the clinical application of the results of the trials and in the direction of future clinical research. These general themes deserve special emphasis.

First, the prophylactic therapies best substantiated by scientific data are substrate-oriented therapies rather than antiarrhythmic therapies per se. We would include in this group of well-substantiated therapies the use of β-blockers in the post-MI patient population as well as the use of angiotensin-converting enzyme inhibitors in some subsets of patients with congestive heart failure. We would also include the use of revascularization in patients with diffuse coronary disease and left ventricular dysfunction in the group of effective therapies, although this treatment measure has not been tested as rigorously as the use of β-blockers post-MI or angiotensin-converting enzyme inhibitors in congestive heart failure. Each of these therapies ameliorates the underlying cardiac pathology. Arrhythmia-focused therapy has failed when employed prophylactically. Whether the morbidity, mortality, and expense of device-based therapy will fare better than treatment with antiarrhythmic drugs remains to be seen.

Second, the mechanisms of action of the effective therapies are poorly understood. It is not known whether the benefits of β-blocking agents are due to their anti-ischemic or antiarrhythmic properties. Nor is the precise mechanism known by which angiotensin-converting enzyme inhibition prevents sudden death. These agents are primarily known for their hemodynamic effects but also have anti-ischemic properties. Treatment of congestive heart failure with angiotensin-converting enzyme inhibitors also influences the autonomic nervous system, which may be important in arrhythmia prevention. The antiarrhythmic agent that currently holds the most promise for sudden death prophylaxis, amiodarone, has very complex cardiac effects. It has a favorable hemodynamic profile in heart failure and was first developed as an antiarrhythmic drug. If this drug is proven to be effective for sudden death prevention, it will be difficult to determine which of these effects is more responsible for the benefit.

Third, risk stratification remains inadequate. In 1994, an outpatient angiogram can confirm the diagnosis of coronary disease in minutes. An echocardiogram can indicate the need for therapy for ventricular dysfunction in even less time. By comparison, selection of patients for sudden death prophylaxis remains inexact; many patients must be subjected to prophylactic medication or device implantation who would not experience sudden death if left untreated. We do not wish to appear overly critical of efforts designed to refine risk-stratification processes. We do wish to highlight the relative lack of understanding of the basic pathophysiology of sudden cardiac death compared with our understanding in other areas of cardiac disease expression. A better basic understanding is crucial if significant breakthroughs are to occur in risk stratification and prophylactic therapy reserved for those patients at greatest risk.

Review of past experience of efforts to prevent sudden death indicates that skepticism regarding new therapies is healthy. This applies to the two treatment modalities currently receiving the most attention, amiodarone and the prophylactic use of implantable devices. Amiodarone has yet to be conclusively shown to be beneficial to patients able to take β-blockers. Furthermore, patients in the large prospective trials will require several years of follow-up before it can be determined whether any treatment benefit outweighs long-term toxicity. While there is little debate that implantable cardioverter-defibrillators prevent sudden death, uncontrolled series have overemphasized the benefits of device therapy. Carefully analyzed controlled trials using total mortality as the primary end point must be completed before the practice of prophylactic device implantation becomes widespread.

Finally, we wish to point out that any small amount of progress toward a clinical solution to the problem of sudden cardiac death has been the product of prospective trials adhering to established scientific principles that have been organized and supported by large numbers of clinicians. This support must continue. The financial burden for this approach is often borne jointly by governmental agencies, the health care industry, and private philanthropy. Progress with this approach has been slow with advances occurring piecemeal. This approach requires patience on the part of health care consumers and their physicians. Nevertheless, until such time that a quantum breakthrough occurs in our understanding of the pathophysiology of sudden death, this is the only approach that has a reasonable chance of success. While progress is expensive, the cost is much less than that of supporting a number of potential therapies that are ineffective or even harmful.

References
