Medical Progress

Sudden Death Due to Cardiac Arrhythmias

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DESPITE a substantial reduction in age-adjusted rates of death from cardiovascular causes during the past 40 to 50 years, cardiovascular disease remains the single most common cause of natural death in developed nations.[1,2] Sudden death from cardiac causes is estimated to account for approximately 50 percent of all deaths from cardiovascular causes.[1,2] The majority of such sudden deaths are caused by acute ventricular tachyarrhythmias, often triggered by acute coronary events, which may occur in persons without known cardiac disease or in association with structural heart disease.[1-3]

Data from clinical electrophysiological studies and randomized trials have led to progress in the identification of patients who are at high risk for death due to arrhythmia. Clinical trials have shown that antiarrhythmic-drug therapy is not effective in reducing mortality among patients who are assumed to be at risk for such death,[4-6] but recent randomized trials have demonstrated a survival benefit in high-risk patients of therapy with an implantable cardioverter–defibrillator, as compared with conventional drug therapy.[7-9] Despite these advances, the effect on the cumulative incidence of sudden death in the population at large has been relatively small, because the majority of sudden deaths occur among patients who do not have the characteristics that would have led to their inclusion in trials of implantable defibrillators (Fig. 1).[2,10] This article is intended to describe the progress in our understanding of sudden death due to arrhythmia, focusing on the methods of prediction and the results and limitations of the various methods and studies of therapy aimed at preventing such deaths.

Mechanisms of Sudden Death from Arrhythmia

Ventricular tachycardia degenerating first to ventricular fibrillation and later to asystole appears to be the most common pathophysiological cascade involved in fatal arrhythmias (Fig. 2).[3,11-13] Bradyarrhythmia or electromechanical dissociation are also frequently recorded as the primary electrical event at the time of sudden death, particularly in patients with advanced heart disease.[14-16] In patients without underlying ischemic heart disease or cardiomyopathy, polymorphic ventricular tachycardia and torsade de pointes caused by various genetic or acquired cardiac abnormalities, such as ion-channel abnormalities, acquired long-QT syndrome, or left ventricular hypertrophy commonly contribute to the initiation of life-threatening arrhythmias.[3] In some cases, such as in patients with the Wolff–Parkinson–White syndrome, atrial fibrillation may lead to especially high ventricular rates and eventually to cardiac arrest.[3]

Two common patterns in the initiation of fatal arrhythmias have been recognized in patients with ischemic heart disease[3,11-13]: ventricular tachyarrhythmia triggered by acute myocardial ischemia in patients with or without preexisting myocardial scarring, and ventricular tachyarrhythmia related to an anatomical substrate (usually scarring from a previous infarction) without active or clinically obvious myocardial ischemia (Fig. 2). Acute myocardial ischemia is generally considered to be the most common factor triggering fatal arrhythmias.[17] In addition to ischemia, several other triggering mechanisms have been recognized, including systemic metabolic and hemodynamic alterations, neurochemical and neurophysiological factors, and exogenous toxic or pharmacologic effects.[1,2,18] These triggering conditions can interact with ischemia, cardiac structural abnormalities, or primary electrophysiological abnormalities, resulting in a complex of factors that can produce sudden death from arrhythmia (Fig. 2).

Epidemiology of Sudden Death from Cardiac Causes

Epidemiologic data indicate that structural coronary arterial abnormalities and their consequences are the cause of 80 percent of fatal arrhythmias (Fig. 2).[1,2,3,18] Dilated and hypertrophic cardiomyopathies account for the second largest number of sudden deaths from cardiac causes.[3] Other cardiac disorders, such as valvular or congenital heart diseases, acquired infiltrative disorders, primary electrophysiological disorders, and the known genetically determined ion-channel abnormalities, account for only a small proportion of the sudden deaths that occur in the general population.[1-3]

Noninterventional, observational studies of risk and interventional trials of therapy directed at the prevention of fatal arrhythmias have been carried out primarily in populations of patients with previously diagnosed ischemic heart disease or heart failure (Fig. 1).[10] It is an epidemiologic paradox that we lack information on specific markers of an increased risk of death from arrhythmia both in the general population and among those with nonspecific and interme-

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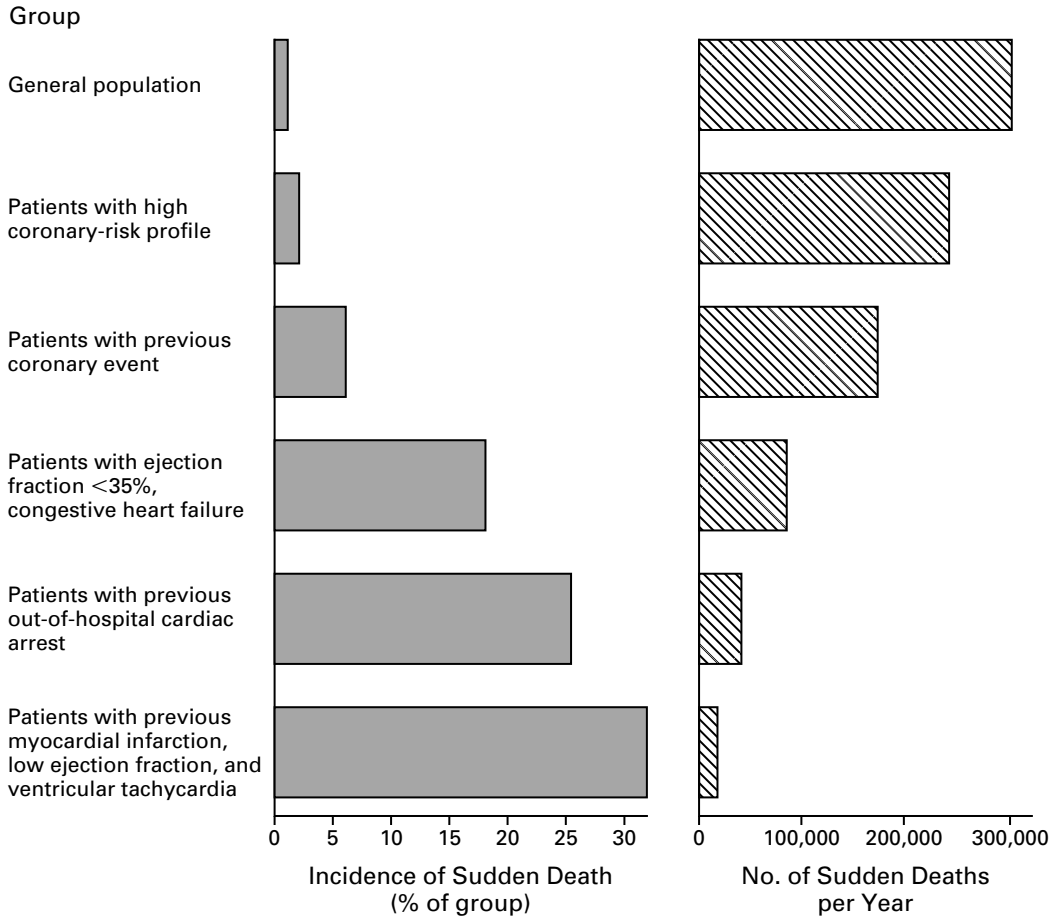

Figure 1. The Incidence of Sudden Death in Specific Populations and the Annual Numbers of Sudden Deaths in Those Populations. Most of the deaths occur in the larger, lower-risk subgroups. Modified from Myerburg et al.[10] with the permission of the publisher.

diate risk profiles, who together account for the largest absolute number of events.

MEASURES OF THE RISK OF LETHAL ARRHYTHMIAS

Common cardiovascular risk factors, such as cigarette smoking, hypertension, and hyperlipidemia, serve as easily identifiable markers of an elevated risk of sudden death from cardiac causes.[1-3] Their limitation is that they primarily identify the risk of the underlying disease that may be responsible for sudden death, rather than the risk of the event immediately responsible for death.[1,2] The usefulness of conventional risk factors in identifying high-risk subgroups in epidemiologic terms is unquestionable, and it is likely that active interventions aimed at prevention will influence some of these risk factors and reduce the number of fatal arrhythmic events. However, the low cumulative value of these common risk markers for predicting such events in individual subjects has stimulated clinicians and scientists to find more specific markers of the risk of death from arrhythmia. The indicators of risk and their value in predicting such death are summarized in Table 1.

Cardiovascular Function

Heart failure, defined as impairment of functional capacity, and left ventricular dysfunction are important determinants of the risk of sudden death from arrhythmia.[19-21] The degree of functional impairment, as categorized according to the New York Heart Association classification, is the simplest variable that can be used to assess the degree of heart failure. Both the degree of functional impairment and the degree of left ventricular dysfunction, as measured with the use of echocardiography, contrast angiography, or iso-

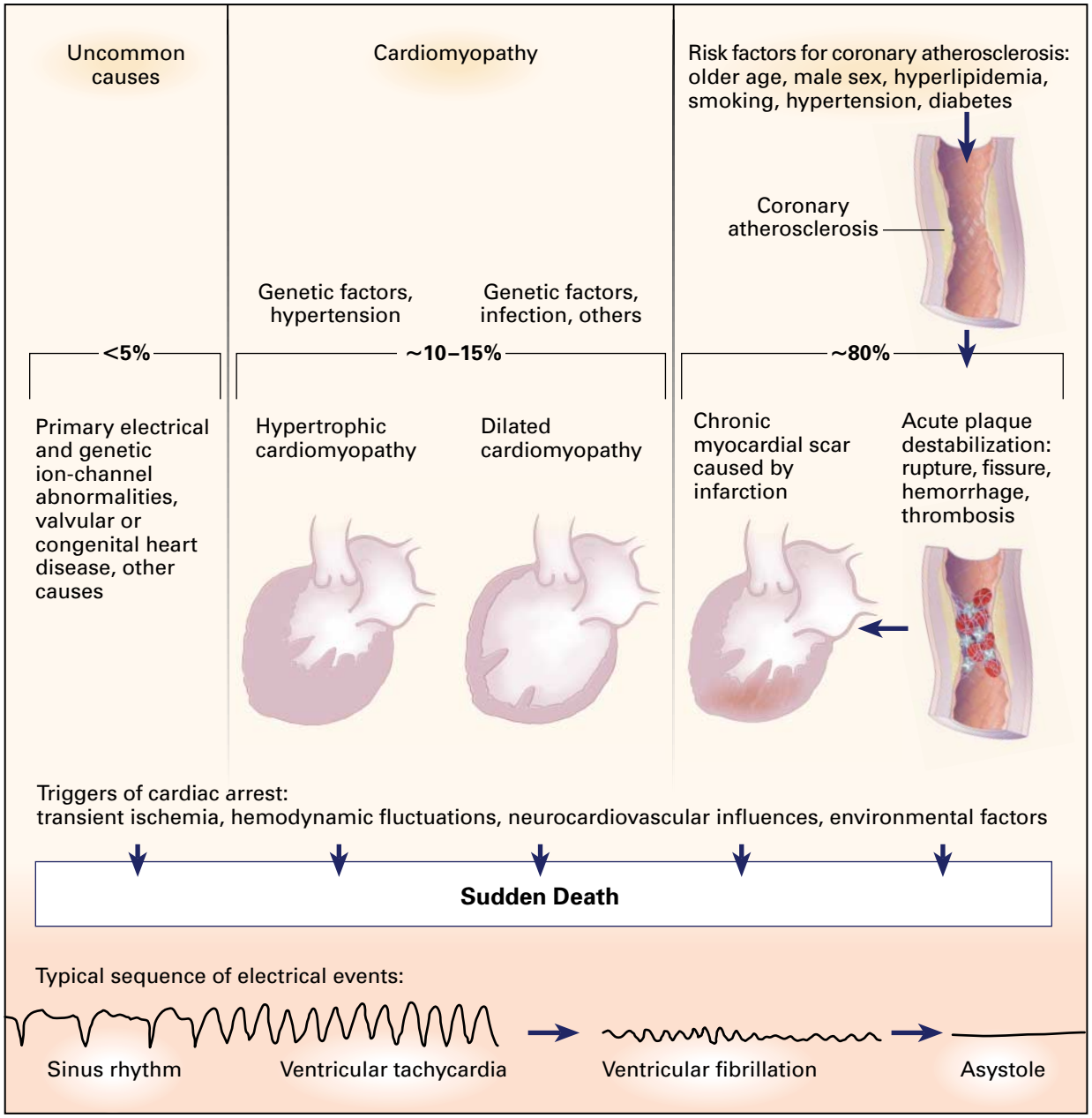

Figure 2. Pathophysiology and Epidemiology of Sudden Death from Cardiac Causes.

tope techniques, are powerful predictors of the risk of death.[1,2,19-21]

Despite the clinical applicability of the assessment of functional class and left ventricular ejection fraction, these methods have limitations as specific markers of the risk of death due to arrhythmia. As the functional impairment increases, total mortality and the absolute number of sudden deaths increase, but the proportion of total deaths due to cardiac arrhythmias decreases.[14,21,22] Thus, the degree of functional impairment and left ventricular dysfunction lack specificity as predictors of death due to arrhythmia because they are also powerful measures of the risk of death from nonarrhythmic causes.

The combination of the measurement of the ejection fraction with the assessment of other risk factors for arrhythmia improves the accuracy of prediction, and most randomized trials have included the meas-

TABLE 1. INDICATORS OF AN INCREASED RISK OF SUDDEN DEATH FROM ARRHYTHMIA.*

VARIABLE	MEASURE	PREDICTIVE POWER
Conventional coronary risk factors	Risk of underlying disease	Low power to discriminate the individual person at risk for sudden death from arrhythmia
High cholesterol		
High blood pressure		
Smoking		
Diabetes		
Clinical markers	Extent of structural disease	High power to predict death from cardiac causes; relatively low specificity as predictors of death from arrhythmia
NYHA functional class		
Ejection fraction		
Ambient ventricular arrhythmia	Presence of transient triggers	
Frequency of premature ventricular depolarizations		Low overall power if not combined with other variables
Nonsustained ventricular tachycardia		
Sustained ventricular tachycardia		Higher predictive power, with low ejection fraction
Electrocardiographic variables	Presence of electrical abnormalities	
Standard ECG		
Left ventricular hypertrophy		Low power to predict death from arrhythmia
Width of QRS complex		
QT dispersion		
Specific abnormalities (e.g., prolonged QT interval, right bundle-branch block plus ST-segment elevation in lead V_1 [Brugada syndrome], ST-segment and T-wave abnormalities in leads V_1 and V_2 [right ventricular dysplasia], delta waves [Wolf–Parkinson–White syndrome])		High degree of accuracy in identifying specific electrical abnormalities
High-resolution ECG		
Late potentials on signal-averaged electrocardiography		High negative predictive value but low positive predictive value
T-wave alternans		Primary predictive value unknown
Markers of autonomic nervous function	Presence of conditioning factors	Exact predictive value unknown
Heart-rate variability		
Baroreflex sensitivity		
Electrophysiological testing	Presence of permanent substrate for ventricular arrhythmias	High degree of accuracy in specific high-risk subgroups
Inducibility of sustained tachyarrhythmia by programmed electrical stimulation		

*ECG denotes electrocardiogram, and NYHA New York Heart Association.

urement of the ejection fraction as part of a predefined assessment of risk.[4-9] Ongoing trials in which patients with a depressed left ventricular ejection fraction are randomly assigned to receive prophylactic therapy with an implantable cardioverter–defibrillator, other antiarrhythmic therapy, or standard therapy for heart failure will define more precisely the role of left ventricular function as a single risk factor for death due to arrhythmia.[23] For now, these estimates have important clinical value only in high-risk subgroups such as persons with documented episodes of sustained ventricular tachycardia or cardiac arrest[8] and patients with a history of unexplained syncope or nonsustained ventricular tachycardia.[7-9]

Ambient Ventricular Arrhythmias

Premature ventricular depolarizations in persons without structural heart disease do not usually increase the risk of initiation of a fatal arrhythmia.[24,25] Thus, the association between premature ventricular beats and ventricular tachyarrhythmias depends on additional influences, referred to as conditioning or triggering factors.[10] More important, the suppression of ambient arrhythmias, recorded on ambulatory monitoring devices, has not been shown to result in improved survival in any of the adequately powered, large-scale studies,[4-6] and in some studies antiarrhythmic drugs have done harm.[4,5] Early observations suggested that frequent premature ventricular depolarizations or episodes of nonsustained ventricular tachycardia, noted during 24-hour Holter recordings, were associated with an increased risk of sudden death among patients with heart failure or a recent myocardial infarction.[20,26-30] However, recent results suggest that such arrhythmias may not provide independent prognostic information in patients with advanced heart failure.[31,32]

There is also a paradox with regard to the relations among the degree of left ventricular dysfunction, the presence of ambient ventricular arrhythmias, and the mechanism of death. The prevalence of both premature ventricular depolarizations and nonsustained ventricular tachycardia is higher among patients with severe heart failure than among those with mild-to-moderate heart failure, but the proportion of patients who die from ventricular tachyarrhythmia is lower in

the former group than in the latter.[22] Together, these data suggest the probability that ambient ventricular arrhythmias reflect the degree of heart failure, rather than serve as specific markers of vulnerability to fatal arrhythmias. Even when ambient ventricular arrhythmia is present in the absence of heart failure, long-term antiarrhythmic therapy for this condition is no longer considered a defined and proven strategy for preventing sudden death from cardiac causes.

In the presence of heart disease, sustained ventricular tachycardia, defined as repetitive sequences lasting 30 seconds or longer, is generally viewed as a marker of increased risk for sudden death from arrhythmia.[25] Sustained ventricular tachycardia can be classified as the monomorphic form, in which each consecutive complex is similar in morphologic features to the others and the rate is relatively constant, or polymorphic, in which there is variation in the beats as well as in the length of the cycles between beats. In the absence of structural heart disease, monomorphic tachyarrhythmias frequently do not indicate an increased risk of fatal arrhythmias.[25] When polymorphic ventricular tachycardias occur as spontaneous clinical events, however, they reflect a higher risk.[25] Another characteristic of tachyarrhythmias that influences risk is hemodynamic stability in their presence. Even for monomorphic forms, tachycardias leading to hemodynamic instability and syncope are considered to reflect higher risk than do tachycardias without hemodynamic instability.[25,33] Finally, without adequate preventive therapy, patients who have had ventricular fibrillation that was not associated with transient causes or an ischemic event have a very high risk of recurrent life-threatening events.[34]

Electrocardiographic Measures of Risk

Standard 12-lead electrocardiography (ECG) is not useful in the ascertainment of risk beyond the reflection of underlying structural heart disease or specific electrophysiological syndromes, such as the long-QT syndrome,[35] right ventricular dysplasia,[36] hypertrophic cardiomyopathy,[37] and the Brugada syndrome (right bundle-branch block and ST-segment elevation in lead V_1).[38] High-resolution processing may permit the analysis of subtle electrocardiographic information on specific markers of risk. These techniques have been applied successfully to both patterns of depolarization (QRS complexes) and repolarization (T waves).[39-44]

In the signal-averaged ECG, high-gain amplification and filtering make possible the detection of small potentials in the terminal part of the QRS complex[39] that are thought to reflect the presence of potential substrates for ventricular tachyarrhythmias. Although the negative predictive value of normal findings on signal-averaged ECG in patients who have had a myocardial infarction has been demonstrated to be excellent, its positive predictive accuracy has been relatively low in most studies,[40-44] a finding that limits its usefulness as a guide to preventive therapy.

Two ECG markers of abnormalities in repolarization have been studied — QT-interval dispersion[45] and T-wave alternans.[46] Measurement of QT-interval dispersion — the difference between the maximal and minimal QT intervals from the various leads on a standard ECG — has been proposed as a method for identifying patients who are at risk for sudden death from arrhythmia.[47-50] However, there are methodologic problems in the accurate measurement of QT-interval dispersion,[51] which may explain why reports on its value as a predictor of death from arrhythmia have been inconsistent.[48-52] The other measure of abnormality in repolarization, T-wave alternans, is defined as alternating T-wave amplitude from beat to beat on the ECG. It is not visible without special ECG recording techniques. Analysis of the amplitude of T-wave alternans at specified heart rates (105 to 110 bpm) suggests that its presence predicts a high risk of life-threatening arrhythmia in specific high-risk patients[53-58]; it is not yet known whether this technique can be applied to larger groups of patients with a low-to-intermediate risk of fatal arrhythmias.

Electrophysiological Testing

The inducibility of sustained ventricular tachyarrhythmia by programmed electrical stimulation is a well-established marker of an increased risk of ventricular tachyarrhythmias.[59,60] In patients with a clinical presentation of sustained ventricular tachycardia or cardiac arrest without an identifiable transient trigger such as acute myocardial infarction, laboratory-inducible ventricular tachycardia has been shown to predict an increased risk of the recurrence of life-threatening arrhythmias.[59-62] Electrophysiological testing also provides clinically useful information for risk stratification in patients with impaired left ventricular function and a clinical presentation of unexplained syncope without a documented arrhythmic event.[63]

The sensitivity and validity of the results of electrophysiological testing seem to be better for patients with a previous myocardial infarction than for those with nonischemic cardiomyopathy.[64] Although the risk of subsequent ventricular tachyarrhythmia can be estimated fairly accurately in the aforementioned groups of high-risk patients, a limitation of this technique is the relatively high number of false negative results. Noninducibility of ventricular tachyarrhythmia may not imply a lack of risk of recurrence of life-threatening arrhythmic events,[9,65] and subsequent sudden death in patients at very high risk cannot uniformly be predicted by this technique. In fact, there is evidence that therapeutic decisions concerning the implantation of cardioverter–defibrillators can be made in the cases of certain high-risk patients without performing an electrophysiological study, and that this approach may be cost effective.[66]

In early applications, the suppression of inducibility of ventricular arrhythmias during the course of an invasive study was also evaluated as a measure of the efficacy of antiarrhythmic-drug therapy.[61,62,64] However, current data suggest that the validity of this strategy is doubtful,[9] and the suppression of inducibility by antiarrhythmic drugs has lost favor as a therapeutic strategy. Nevertheless, knowledge of the inducibility of ventricular tachyarrhythmia by programmed electrical stimulation is still considered useful for clinicians making therapeutic decisions regarding such matters as a patient's candidacy for implantation of a cardioverter–defibrillator.

Electrophysiological testing has also been used for risk stratification in patients without a history of ventricular tachyarrhythmia or unexplained syncope. The test has little positive predictive accuracy for the identification of patients with recent myocardial infarction who are prone to ventricular tachycardia.[67,68] Promising data on the value of programmed electrical stimulation have been obtained from two randomized trials,[7,9] both of which show that prophylactic therapy with implantable cardioverter–defibrillators improves the prognosis of patients with nonsustained ventricular tachycardia, reduced ejection fraction, and inducible ventricular tachyarrhythmia. On the basis of the results of these studies, electrophysiological testing is now widely recommended for patients with a reduced ejection fraction who have had episodes of nonsustained ventricular tachycardia.

Variability in Heart Rate and Baroreflex Sensitivity

Several experimental and clinical observations support the notion that the autonomic nervous system has a role in the genesis of fatal cardiac arrhythmias.[69] Variability in heart rate reflects both sympathetic and parasympathetic outflow to the heart and has been extensively studied during the past decade for its value as a predictor of sudden death from cardiac causes.[70-78] The measurement of baroreflex sensitivity, an indicator of the reflex capacity of the autonomic nervous system, has also been studied in the context of risk stratification with respect to arrhythmic events.[75] Reduced variability in the heart rate over a 24-hour period, measured as the standard deviation of RR intervals, and baroreflex sensitivity as measured by means of a phenylephrine test have had relatively low accuracy as predictors of arrhythmic events, but in combination with other test results these measures have somewhat higher accuracy.[70-78] The clinical applicability of these variables for stratification of the risk of death from arrhythmia must be established in future randomized trials.[76]

PREVENTION OF SUDDEN DEATH

Primary-Prevention Trials

Therapeutic strategies for the prevention of sudden death from cardiac causes may be divided into two general categories — primary prevention and secondary prevention. Primary prevention refers to the prevention of the first life-threatening arrhythmic event, such as sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest. Secondary prevention refers to the prevention of a recurrence of a potentially fatal arrhythmia or cardiac arrest among patients who have had clinical events of that type.[10] Within each category, the two most commonly applied specific strategies are the use of antiarrhythmic drugs and the use of implantable cardioverter–defibrillators. Ancillary approaches, such as catheter-based or surgical revascularization and various types of ablation procedures, have not been as well studied. The characteristics of target populations, study designs, and results of trials of primary and secondary prevention are summarized in Table 2.

The earliest primary-prevention trials tested whether beta-blocker therapy in patients who had had a myocardial infarction would provide a survival benefit.[79,80] Although not designed specifically to evaluate the risk of sudden death, most of these trials identified a reduction in the incidence of sudden death with beta-blockade, especially among patients with lower ejection fractions.[79-81] When primary-prevention trials of antiarrhythmic therapy in patients who had had a myocardial infarction were specifically targeted to the assessment of the risk of sudden death from cardiac causes, conflicting results were obtained. The most dramatic of these trials was the Cardiac Arrhythmia Suppression Trial,[4] which tested the hypothesis that patients who had had a myocardial infarction and had drug-suppressible premature ventricular depolarizations would derive a survival benefit from antiarrhythmic-drug therapy.[4] The drug-treated group had a markedly increased risk of death due to arrhythmia, at least among the patients receiving class IC antiarrhythmic agents (i.e., encainide or flecainide). Another trial, the Survival with Oral *d*-Sotalol Trial, tested the effect of *d*-sotalol, a sotalol isomer without a beta-blocking effect, and also demonstrated an adverse outcome.[5]

In the early 1990s, two major trials of amiodarone in patients who had had a myocardial infarction — the European Myocardial Infarct Amiodarone Trial[82] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial[83] — demonstrated no survival benefit, even though there was an apparent antiarrhythmic benefit.[82,83] Subsequent analyses have suggested that in both studies, the concomitant use of beta-blockers and amiodarone did provide a survival benefit.[84] This hypothesis needs to be tested in a prospective trial before it can be accepted. Because this series of studies suggested, at best, no effect on overall survival and, at worst, an adverse effect of antiarrhythmic drugs used for primary prevention, the popularity of this therapeutic approach for patients who have had a myocardial infarction has faded. The only approach

TABLE 2. STRATEGIES FOR THE PRIMARY AND SECONDARY PREVENTION OF SUDDEN DEATH FROM CARDIAC CAUSES.

PREVENTIVE STRATEGY	EJECTION FRACTION (%)	OTHER CLINICAL CHARACTERISTICS	LEVEL OF RISK	STUDY DESIGN	RECOMMENDED TREATMENT
Prevention of cardiac arrest in patients with advanced coronary artery disease and previous myocardial infarction	≤40	NYHA class I, II, or III*	Variable	Randomization, placebo control, subgroup analysis	Beta-blockers
	≤40	Nonsustained ventricular tachycardia; inducible ventricular tachycardia	High	Randomization, active-treatment control	Implantable cardioverter–defibrillator
Prevention of recurrent cardiac arrest in patients with advanced structural disease (coronary artery disease or dilated cardiomyopathy)	≤35	Ventricular tachycardia, ventricular fibrillation or unexplained syncope plus inducible ventricular tachycardia	High	Randomization, active-treatment control	Implantable cardioverter–defibrillator

*The magnitude of the benefit is uncertain in patients with New York Heart Association (NYHA) class I disease.

with an accepted survival benefit at this time is beta-blocker therapy.

There has also been interest in the use of drugs for primary prevention that may halt or delay the progress of cardiac disease or prevent the occurrence of acute ischemic events. At present, it is difficult to evaluate the contribution of commonly used drugs, such as aspirin, angiotensin-converting–enzyme inhibitors, and statins, to the prevention of sudden death from cardiac causes. Because of low intrinsic mortality rates among the study populations, such studies are not sufficiently powered to identify whether there is a reduction in the incidence of death from arrhythmia. They are better powered to identify benefits in reducing cardiovascular morbidity and perhaps mortality in patients with preexisting clinical manifestations of heart disease.[10]

Other primary-prevention trials have focused on a comparison between therapy with implantable cardioverter–defibrillators and drug therapy.[7,9] Three large-scale, randomized trials aimed at reducing mortality by means of prophylactic cardioverter–defibrillator therapy have been completed.[7,9,85] Two tested the hypothesis that therapy with this type of device results in lower mortality than antiarrhythmic-drug therapy,[7,9] and the third compared cardioverter–defibrillator therapy with standard therapy.[85] Two of the trials, the Multicenter Automatic Defibrillator Implantation Trial[7] and the Multicenter Unsustained Tachycardia Trial,[9] which used similar predefined risk variables (including a reduced left ventricular ejection fraction, documented nonsustained ventricular tachycardia, and inducibility of sustained ventricular tachycardia during programmed electrical stimulation), showed that prophylactic cardioverter–defibrillator therapy reduces mortality. The third trial, the Coronary Artery Bypass Graft Patch Trial,[85] used a surrogate marker of arrhythmia — a positive signal-averaged ECG — rather than manifest or inducible arrhythmias, to stratify patients for randomization to cardioverter–defibrillator therapy or standard therapy after they had undergone coronary revascularization surgery. That study did not identify a benefit from prophylactic cardioverter–defibrillator therapy, a fact that emphasizes the importance of specific markers of risk and the selection of patients in this type of trial.

According to the results of the trials investigating the prophylactic use of cardioverter–defibrillators, the presence of nonsustained ventricular tachycardia and inducible sustained ventricular tachycardia in patients with a reduced ejection fraction (less than 40 percent) is an indication for implantation of the cardioverter–defibrillator. A practical problem limiting the application of the findings of these published randomized trials is that there are no data on the proportion of patients who would fulfill the inclusion criteria, because the size of the total population of patients with the appropriate indications is unknown.[86,87] Preliminary reports suggest that only a small proportion of the consecutive patients with a previous myocardial infarction would fulfill the inclusion criteria for these trials.[88] Therefore, it remains unclear whether screening patients with impaired left ventricular function routinely for prophylactic cardioverter–defibrillator therapy is clinically feasible and cost effective.

The primary prevention of arrhythmias that may lead to sudden death remains problematic. Two studies support the idea that for a small but very high-risk subgroup, prophylactic cardioverter–defibrillator therapy provides a benefit over drug therapy, and this therapeutic strategy is gaining general acceptance.[89] This high-risk subgroup consists of patients with nonsustained ventricular tachycardia and inducible sustained ventricular tachycardia with a reduced ejection fraction. At the other end of the spectrum, in more general populations of patients who have had a myocardial infarction and in other groups of patients such as those with dilated cardiomyopathy, no predictable and significant benefit of prophylactic ther-

apy has been identified. As far as drug therapy is concerned, beta-blocker therapy, although nonspecific, is the only generally accepted therapeutic approach for the primary prevention of life-threatening arrhythmia.

Secondary-Prevention Trials

There is no evidence from trials that drug treatment, including the use of beta-blockers and amiodarone, or surgical interventions, such as coronary-artery bypass graft surgery or ablation procedures, prevent the recurrence of life-threatening arrhythmic events. Despite the lack of scientific evidence, these therapeutic strategies are commonly used in selected individual cases, on the basis of empirical assessment and clinical judgment.

The only evidence-based therapeutic strategy for patients who have survived a life-threatening arrhythmic event is the implantation of a cardioverter–defibrillator. The first secondary-prevention trial, the Antiarrhythmics versus Implantable Defibrillators (AVID) Trial,[8] demonstrated a survival benefit of cardioverter–defibrillator therapy as compared with antiarrhythmic-drug therapy among patients with a previous life-threatening arrhythmic event and depressed left ventricular function. Similar results have been reported in two smaller randomized trials, the Canadian Implantable Defibrillator Study and the Cardiac Arrest Study Hamburg.[90,91] In a subgroup analysis of the AVID data base, it was observed that among patients with better-preserved left ventricular function — ejection fractions in the range of 35 to 40 percent — cardioverter–defibrillator therapy had no advantage over drug therapy.[92] This was a secondary analysis, however, which suggests but does not prove that cardioverter–defibrillator therapy fails to provide a survival benefit in this subgroup.

FUTURE DIRECTIONS

A challenge for the future is the development of new approaches or techniques that will allow screening for markers of increased risk of fatal ventricular arrhythmias in large general populations, in which the relative risk is low but the number of deaths due to arrhythmia is high.[1] Among the candidates for better strategies is the possibility of identifying genetic factors that can be used to stratify the at-risk populations into groups with sufficiently high risk to warrant complex and advanced therapies. Recent epidemiologic surveys suggest that there is a specific risk of sudden death from cardiac causes as an initial manifestation of acute myocardial infarction when there is a history of familial clustering of such events.[93,94] This finding implies that there may be genetic factors conditioning the susceptibility of an individual patient with a specific genetic pattern to an arrhythmic response to ischemia.[95]

A pessimistic view of the usefulness of various methods of predicting death due to arrhythmia is that the onset of fatal arrhythmia is a random phenomenon that cannot be predicted by the commonly used markers. The alternative view is that the cascade leading to sudden death from arrhythmia can be predicted by subtle interactions among structural and functional abnormalities. The latter hypothesis has tempted scientists to apply the concepts of chaos theory to the study of arrhythmia and to clinical medicine.[96,97] The basic concept of the theory is that seemingly random dynamic events, such as ventricular fibrillation, may in fact arise from minute fluctuations in deterministic systems — those in which there is a sensitive dependence on initial conditions — so that small perturbations may be magnified exponentially.[96] The concepts of chaos theory are still far from providing practical answers for clinical medicine but may indicate a fruitful direction for future research. A search for new tools for prediction, the refinement of the existing tools, and the initiation of well-designed intervention trials are the steps that must be taken toward the more efficient prevention of premature sudden deaths from arrhythmia.

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