Prediction of Sudden Cardiac Death
Appraisal of the Studies and Methods Assessing the Risk of Sudden Arrhythmic Death

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Since the recognition of the high incidence of cardiac arrest as the mechanism of sudden cardiac death (SCD), medical scientists and clinicians have sought methods to predict and prevent these events. Significant progress has already been made in the prediction and prevention of life-threatening arrhythmias during the last decade. This progress is highlighted by the outcomes of 4 recently published randomized studies demonstrating that the implantable cardioverter defibrillator (ICD) provides a mortality benefit compared with conventional drug therapy in highly specific subsets of patients.1–4 In parallel with intervention studies, several observational studies and reports have raised an optimistic notion that arrhythmic death can be predicted by methods potentially useful for widespread screening programs.5–10

Despite the evidence-based data and practical recommendations for indications of ICD therapy,11 utilization of this therapy has not been uniformly implemented worldwide, and screening of patients at potential high risk for arrhythmic death has not become a routine clinical practice. In addition to economic and educational factors, this may be due to methodological problems in the designs of a number of the completed observational and randomized intervention studies that confound the interpretation of the results and general application of the procedures. In this report, we analyze the problems of predicting arrhythmic deaths and the advantages and limitations of the various methods and studies, and we evaluate the need for new and better studies and methods of risk stratification.

Study Designs
Three types of clinical research designs have been used to estimate the efficacy of interventions and the accuracy of methods for predicting sudden arrhythmic death: (1) observational follow-up studies, (2) case-control studies, and (3) randomized intervention designs.

Observational studies are based on baseline assessment of 1 or more risk variables and subsequent follow-up of predefined patient groups. These studies have been most commonly used in the assessment of the predictive power of variables thought to predict arrhythmic deaths.5–10 In case-control studies, outcomes of an intervention are compared between survivors of documented arrhythmic events and matched control subjects without a history of life-threatening arrhythmia.12,13

A randomized ICD trial is the most reliable way to document the impact of an intervention targeted to a predefined arrhythmia risk variable. In antiarrhythmic trials, the patients are randomly assigned to the intervention group and either to a placebo or a positive (alternative active therapy) control group. Many placebo-controlled antiarrhythmic drug trials have been completed in predefined patient groups,14 but none of these trials has reported a benefit from antiarrhythmic drugs in reduction of all-cause mortality. More recently, several large-scale randomized trials aimed at reducing arrhythmic mortality by ICD therapy have been completed,1–4,15 all testing the hypothesis that ICD therapy reduces mortality compared with antiarrhythmic drug therapy or conventional heart failure therapy in patients with a predefined risk of arrhythmic death. Two of the trials (Multicenter Automatic Defibrillator Implantation Trial [MADIT] I and Multicenter UnSustained Tachycardia Trial [MUSTT]),1,3 which used similarly predefined risk variables, showed that prophylactic ICD therapy reduces mortality. The Coronary Artery Bypass Graft (CABG) Patch trial,15 which used different risk variables, did not identify benefit from the prophylactic ICD therapy. Finally, the most recent trial (MADIT II) showed that ICD therapy reduces mortality among the patients with a reduced ejection fraction, without specific arrhythmic markers, compared with those with standard therapy.4

Methodological Problems and Biases Related to the Study Designs
All of the above study designs are susceptible to methodological problems. The potential biases in the study designs can be epidemiological or economic, or they may be related to the selection of the patients or the predefined end point of the study. The impact of these biases on clinical applicability of
the results of the studies investigating the SCD risk is largely dependent on the study design. Observational studies are confounded by almost all the biases. Case-control studies lack some of the problems of observational studies, eg, end-point bias, but a selection bias also exists in case-control studies, because survivors of arrhythmia may differ from those who die. The randomized trials lack many of the biases, but a practical problem with the published trials showing the benefit of prophylactic ICD therapy is that there are no definite data on the prevalence of patients fulfilling the inclusion criteria, because the denominator of the patient populations studied in the prophylactic ICD trials is unknown. It is possible that patients included in these studies may represent a specific subgroup consulting healthcare professionals in tertiary hospitals because of symptoms or worsening of their health status. Despite the screening logs and registries in some of the trials, the true incidence of the patients who are similar to those randomized to these trials is largely unknown in the general population, and the need for routine screening of the patients for prophylactic ICD therapy and the cost efficacy of the screening are also unknown.

Epidemiological Bias
Nonintervention observational studies of risk, and intervention trials of therapy directed to prevention of fatal arrhythmias, have been carried out primarily in populations of individuals with a previous myocardial infarction. There is a lack of information on specific risk markers and preventive strategies of SCD among the lower-risk populations, which account for the largest absolute number of events. Consequently, the efficiency of risk evaluation in more general populations is largely unknown, and the evidence-based prophylactic therapy, eg, by ICDs, has probably not had a major impact on the overall number of SCDs. For example, a recent survey from the United States showed that there was only a minor decline in the absolute number of SCDs in the 1990s despite a significant increase in the number of ICD implants. In fact, the proportion of cardiovascualr deaths that are sudden increased during that period.

Selection Biases
Patients entering studies designed to estimate the risk for arrhythmic death do not always represent a consecutive series with predefined characteristics, as called for in the study design, because of selection and exclusion criteria intended to make the test or intervention more suitable on the basis of ethics or science. For example, an evaluation of the registry of the Antiarrhythmic Versus Implantable Defibrillators (AVID) trial documented that the mortality rate of those patients who were excluded from the study was higher than the mortality of the patients randomized to ICD therapy. Published articles frequently do not report the results of the randomly or nonrandomly excluded patients, and this has limited generalization of the results to other populations.

End-Point Bias
A problem in interpreting the results of observational studies is the inaccuracy of the definition of sudden arrhythmic death, as all definitions suffer from a possibility of misclassification of the precise mode of death. Sudden death occurring within an hour of the onset of symptoms has been commonly attributed to arrhythmia, but many other pathophysiological conditions that evolve rapidly can also lead to sudden death. Recent studies on patients with ICD indicate that many of the deaths defined as sudden were not due to tachyarrhythmia. In some cases, ventricular tachyarrhythmia was a terminal epiphhenomenon, confounding mechanical dysfunction as the cause of a sudden death. The definitions of arrhythmic events also tend to vary in observational studies, because some of them equate SCD with resuscitated ventricular fibrillation, whereas others use sustained ventricular tachycardia, resuscitated ventricular fibrillation, and sudden death as a combined end point. The mechanisms and risk factors of ventricular fibrillation and sustained monomorphic ventricular tachycardia may differ, and resuscitated ventricular fibrillation victims may differ inherently from those who die during the event.

Concomitant Treatment Bias
Clinical trials have convincingly shown that many medical and other treatment strategies, such as thrombolytic treatment, revascularization therapy, aspirin, angiotensin-converting enzyme inhibitors, and statins, will influence the outcome of cardiac patients. In addition to reduced overall mortality, β-blocking therapy has been shown to reduce the incidence of SCD, particularly among patients with depressed left ventricular function. Therefore, the predictive power of arrhythmia risk variables, based on studies of populations without the optimal treatment, may no longer be valid among the patients treated with therapies that were not available at the time of these studies.

Economic Bias
Healthcare costs have been rapidly rising in Western societies. It is obvious that economic issues have significantly influenced the adherence to ICD therapy. For example, wide variations exist between the nations in the rate of ICD implants, which is 3- to 4-fold higher in the United States as compared with many Western European countries (Table 1). The cost-effectiveness analyses of ICD studies suggested that this therapy is “economically attractive” compared with many other previously accepted therapies, such as dialysis for end-stage renal failure. However, there simply may not be enough financial resources available in many societies to pay for a new therapy, regardless of how cost effective the therapy is.

Publication Bias
Both observational and randomized studies are also sensitive to publication bias. Many negative studies may remain unpublished and thereby create a bias for reliable interpretation of the results, particularly in meta-analyses of the studies.

Duration of Follow-Up
Differences in the follow-up times of the observational and randomized trials also create a potential bias for the comparison and interpretation of various studies. If the follow-up is too brief, the event rate may remain too low for reliable conclusions about the accuracy of test results. On the other
hand, the temporal changes in the risk variable profiles due to progression of disease itself, and the eventual convergence of all survival curves, limit the long follow-up times.

Prognostic Value and Limitations of the Arrhythmic Risk Markers

A large number of studies designed to assess the risk markers of sudden arrhythmic death have been published in the medical literature during the last decade. The most extensively studied arrhythmia risk markers, the main outcome of studies, and the potential biases of the methods and studies are summarized in Table 2 and discussed below.

Cardiovascular Function

The degree of functional impairment (typically classified by the New York Heart Association schema) and the severity of heart damage reflected by the left ventricular ejection fraction are the simplest variables used for the assessment of the loss of cardiac reserve and prognosis of patients with structural heart disease. Despite the clinical applicability of assessment of functional class and of left ventricular ejection fraction by echocardiography, these methods have some potential limitations as specific risk markers of arrhythmic death. The degree of functional impairment, the degree of left ventricular dysfunction, and the prevalence of fatal arrhythmias are not linearly related, as the proportion of sudden death from total cardiac mortality is higher among the patients with mild-to-moderate heart failure than in those with severe heart failure. However, the absolute event rate of SCD is still higher among the patients with severe heart failure because of a higher incidence of overall cardiac mortality.

Despite these limitations, a recent prophylactic, randomized ICD trial (MADIT II) demonstrated that measurement of the left ventricular ejection fraction provided clinically important information on the risk of arrhythmic mortality. Another ongoing trial, Sudden Cardiac Death in Heart Failure (SCD-HeFT), in which patients with depressed left ventricular ejection fraction and functional class II or III are randomized to prophylactic ICD therapy versus amiodarone and standard heart failure therapy, will further define the role of cardiovascular function as a risk marker of arrhythmic death. Nevertheless, even after the results of the SCD-HeFT trial are determined, there will still be a lack of information about the role of ICD therapy among the patients with an ejection fraction between 35% and 40%, which constitutes a relatively large proportion of postinfarction patients who are at risk of experiencing a sudden arrhythmic death, and further studies may still be needed among this patient subgroup.

Ambient Ventricular Arrhythmias

Many studies, beginning in the 1970s, reported an increased risk of SCD among the post-myocardial infarction patients, who had frequent premature ventricular depolarizations or episodes of nonsustained ventricular tachycardia (nsVT) during ambulatory ECG recordings. More recently, the popularity of counting of premature ventricular depolarizations from Holter recordings has faded mostly because the suppression of ambient arrhythmias has not been shown to result in improved survival in any of the adequately powered large-scale studies. Results from 2 prophylactic ICD trials suggested that patients with impaired left ventricular function and nsVT episodes should undergo invasive electrophysiological testing for evaluation of candidacy for ICD. To our understanding, routine screening for nsVT among the patients with an ejection fraction <0.40 has not been widely advocated, perhaps because of the doubts about the cost effectiveness of this approach.

Electrocardiographic Measures

Measurements of the length of the QRS and QT intervals from a standard 12-lead ECG are simple and inexpensive methods of risk assessment. It will be important that future studies try to confirm the predictive power of these simple measures of risk. The measurement of QT dispersion seems to have little utility in risk stratification for arrhythmic events because of the technical issues related to its measurement and the negative results from recent observational studies.

Analysis of microvolt-level T-wave alternans, which is not visible without special ECG recording techniques, has been introduced as a new approach for evaluating the risk of life-threatening arrhythmias. Most of the studies assessing the predictive value of positive T-wave alternans have included only high-risk patients, and it is yet not known whether these promising observations can be applied to larger patient groups, such as those with a low to intermediate risk of fatal arrhythmias. A recent study, including postinfarction patients with β-blocking medication, could not confirm the predictive value of these methods in the risk assessment of mortality. Therefore, more research is needed to establish the predictive power of T-wave alternans in adequately defined patient groups.

Signal-averaged ECG is an extensively studied method for predicting arrhythmic events. The negative predictive value

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<tr>
<th>Country</th>
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<tr>
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*Data were obtained from Seah Nisam (Quidant Co; personal communication, September 15, 2002).
of a normal signal-averaged ECG has been high in observational studies, but positive predictive accuracy has been relatively low. The absence of an ICD benefit in the prophylactic ICD trial, CABG Patch, in which late potentials in signal-averaged ECG were used as a predictor of risk for sudden arrhythmic death, has tempered enthusiasm for this method in the stratification of the risk of arrhythmic mortality. However, the definitive role of signal-averaged ECG is difficult to define on the basis of this trial, because there are many other plausible explanations for the lack of efficacy of ICD; eg, the risk of nonarrhythmic mortality risk was relatively high. Furthermore, a more recent study suggested that signal-averaged ECG is a powerful predictor of outcome in the MUSTT population.

### Autonomic Markers
Heart rate variability (HRV) and baroreflex sensitivity have been extensively studied during the last decade for their value as predictors of total mortality, SCD, and the occurrence of ventricular tachyarrhythmias. The value of HRV measurement as a predictor of ICD therapy will be assessed in the ongoing Defibrillation IN Acute Myocardial Infarction Trial (DINAMIT) study, in which the patients with reduced ejection fraction and reduced HRV are randomized to ICD therapy versus conventional therapy.

### Electrophysiological Testing
Programmed ventricular stimulation is a useful test in risk stratification and estimation of the candidacy for ICD among the patients with a prior myocardial infarction and clinical presentation of sustained wide complex tachycardia or unexplained syncope. In patients with spontaneous sustained ventricular tachycardia, the ICD may be useful not just for prevention of sudden death but primarily to aid in the management of those patients, eg, termination of ventricular tachycardia by antitachycardia pacing, and avoidance of pharmacological antiarrhythmic therapy. In addition, the 2 prophylactic ICD studies showed that electrophysiological testing is also useful among the patients with left ventricular dysfunction and occurrence of nsVT on ECG recordings.
Proposal for future attempts to reduce the incidence of sudden arrhythmic death.

However, a positive predictive accuracy of inducibility of ventricular tachycardia alone has been relatively low in consecutive series of patients with recent myocardial infarction.39,40

**Specificity of the Arrhythmia Risk Variables**

From a clinical standpoint, it would be important to compare the clinical utility of various arrhythmia risk markers, eg, their relative specificity and accuracy to predict sudden or arrhythmic death in comparison with total mortality. Unfortunately, there are no large-scale studies comparing the accuracy of various arrhythmia risk markers in risk stratification of the patients in the current treatment era. A recent study in postinfarction patients suggests that all common arrhythmia risk variables have limited accuracy in predicting the occurrence of SCD among the patients treated according to contemporary guidelines, eg, with β blockers.41 Some observational studies have suggested that combination of some risk variables, eg, autonomic markers and ejection fraction,9 may improve the specificity, but the clinical utility of these approaches in risk stratification must still be proven in future trials.

**Future Directions**

It is probable that the incidence of unexpected sudden death can be reduced by a combination of several approaches aimed at preventing its occurrence (Figure). Integrative basic and clinical research may open new strategies both for risk stratification of larger patient groups and for new therapeutic options.42 Primary prevention of underlying heart disease, and more widespread implementation of evidence-based therapy of cardiac patients, eg, autonomic markers and ejection fraction,9 may improve the specificity, but the clinical utility of these approaches in risk stratification must still be proven in future trials.

Avoid selection bias, eg, a consecutive series of patients surviving an acute myocardial infarction; (2) include careful cost-effectiveness analysis, including screening of the patients, as one of the major end points; and (3) optimize the medical and other evidence-based therapy of the patients. In addition, the new trials should include all known risk variables as well as new variables, eg, markers of inflammation and other biomarkers of contributors and progression of coronary heart disease,33,44 natriuretic peptides,45 genetic variables,46 and new ECG markers,47 in the study designs to allow the identification of subgroups of patients with very high risk who might benefit from therapeutic interventions.

One of the challenges is to develop approaches or techniques that will allow screening for risk of fatal ventricular arrhythmias among the general population. Some epidemiological surveys suggest that SCD, as an initial manifestation of coronary artery disease, may cluster in families.48,49 Thus, it is likely that there are genetic or environmental factors, operating along the entire cascade of coronary heart disease evolution,50 conditioning the response to ischemia in a manner that increases the susceptibility of the patient to a lethal arrhythmic response. If specific genetic patterns46 or other factors, eg, markers of inflammation,44 predisposing to ischemic sudden death are discovered in the future, these observations may offer the opportunity to identify high-risk subjects within the general population and to apply preventive strategies far in advance of their development of acute ischemic or other triggering events for fatal arrhythmias.

Despite the progress in the field of prediction and prevention of SCD, adequately designed studies will still be needed for reliable testing of the clinical utility of known risk variables for the prediction of arrhythmic death. New approaches will also have to be added to conventional risk factors to obtain new insight into the potential factors leading to fatal arrhythmias. It is premature to conclude that the occurrence of sudden arrhythmic death is a random phenomenon that cannot be predicted or prevented.

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**References**


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