

EXPERT CONSENSUS DOCUMENT

American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death

A Scientific Statement From the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention

Jeffrey J. Goldberger, MD, FAHA, FACC, FHRS; Michael E. Cain, MD, FAHA, FACC, FHRS;
Stefan H. Hohnloser, MD, FACC; Alan H. Kadish, MD, FAHA, FACC;
Bradley P. Knight, MD, FACC; Michael S. Lauer, MD, FAHA, FACC;
Barry J. Maron, MD, FACC; Richard L. Page, MD, FAHA, FACC, FHRS;
Rod S. Passman, MD, MSCE, FACC; David Siscovick, MD, MPH;
William G. Stevenson, MD, FAHA, FACC, FHRS; Douglas P. Zipes, MD, FAHA, MACC, FHRS

The International Classification of Diseases, Tenth Revision, defines sudden cardiac death (SCD) as death due to any cardiac disease that occurs out of hospital, in an emergency department, or in an individual reported dead on arrival at a hospital. In addition, death must have occurred within 1 hour after the onset of symptoms. SCD may be due to ventricular tachycardia (VT)/ventricular fibrillation (VF), asystole, or nonarrhythmic causes (1). For the purpose of this scientific statement on noninvasive risk stratification for primary prevention of SCD, SCD will specifically refer to death due to reversible ventricular tachyarrhythmias, because this is the focus of the risk stratification techniques to be discussed. Among patients with SCD, an overwhelming majority have some form of structural heart disease; this

statement will be limited to risk stratification techniques for ischemic, dilated, and hypertrophic cardiomyopathies. Although other types of structural heart disease and inherited ion channel abnormalities are also associated with a risk for SCD, the risk stratification strategies and data in these entities are diverse and are beyond the scope of this document.

The annual incidence of sudden arrhythmic deaths has been estimated between 184 000 and 462 000. The American Heart Association has promoted the concept of the “chain of survival,” which includes early access to medical care, early cardiopulmonary resuscitation, early defibrillation, and early advanced care. Many of these interventions have improved survival. Despite all of these advances, however, overall mortality from a cardiac arrest remains high, which under-

The American Heart Association, the American College of Cardiology Foundation, and the Heart Rhythm Society make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on February 4, 2008, by the American College of Cardiology Foundation on February 26, 2008, and by the Heart Rhythm Society on December 11, 2007.

The American College of Cardiology Foundation requests that this document be cited as follows: Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman R, Siscovick D, Stevenson WG, Zipes DP. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *J Am Coll Cardiol* 2008;52:1179–99.

This article is copublished in the September 30, 2008, issue of *Circulation* and the October 2008 issue of *Heart Rhythm*.

Copies: This document is available on the World Wide Web sites of the American Heart Association (my.americanheart.org), the American College of Cardiology (www.acc.org), and the Heart Rhythm Society (www.hrsonline.org). For copies of this document, please contact Elsevier Inc. reprint department, fax (212) 633-3820, e-mail reprints@elsevier.com.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American College of Cardiology Foundation. Please contact Elsevier's permission department at healthpermissions@elsevier.com.

scores the need for risk stratification techniques to identify patients at high risk for these events and effective interventions that can prevent or abort these events. Although risk stratification techniques have been studied for decades, their current relevance is enhanced by the availability of medical therapies (2) and the implantable cardioverter defibrillator (ICD), which have been shown to reduce both total and SCD mortality in selected high-risk patients.

In general, risk stratification techniques have been applied to dichotomize patients into low- and high-risk groups. In actuality, risk is a continuum. Furthermore, it has been noted (3) that the majority of episodes of SCD actually occur in those with low- to intermediate-risk factors and those without known risk factors. The highest-risk subgroups, on which much attention is focused because of the magnitude of the risk of death, actually constitute only a small proportion of the total number of deaths annually. Thus, a comprehensive approach to risk stratification must account for these epidemiological realities. Specifically, risk stratification involves a process of identifying subjects at relatively high risk for later major events. Although it is a widely accepted approach within the ethos of modern medicine, it must be recognized that there are critical weaknesses to this process. For example, the United Kingdom Heart Disease Prevention Project (4) addressed the question of prevention of myocardial infarction (MI). Among all men, the absolute risk of later MI over a 5-year period is low, under 5%. If one focuses on men with risk factors, the absolute risk increases to 7%, which corresponds to a relative risk of ≈ 1.75 . However, this only accounts for 32% of all MIs that occur. If one further focuses on a higher-risk group with risk factors plus early disease, the absolute risk is much higher, 22%, which corresponds to a relative risk of 5.5. Despite these higher absolute and relative risks, however, this group only accounts for 12% of all MIs. As Rose (5) has argued, defining risk narrowly may identify selected individuals for whom interventions are more likely to be beneficial but that do little for society as a whole.

Recognizing these limitations, it is worth delineating the desirable features of a risk stratification tool for SCD. The ideal risk stratification tool would identify most of the patients who will experience VT or VF and exclude those who will not. In addition, intervention (medical, surgical, or ICD) based on an abnormal result should improve survival to a greater extent than does intervention in similar patients with a normal result. The potential for finding such a tool may be hampered by the fact that many tools provide prognostic information on SCD and non-SCD. The utility of a tool to provide risk stratification for SCD will depend on the extent of prognostic information regarding non-SCD. In addition, SCD, defined by the usual criteria, is not always due to VT or VF, and its cause can be difficult to ascertain. For practical reasons, many studies, particularly randomized clinical trials, use an end point of total mortality. To validate the utility of a risk stratification tool that is specific for SCD, it is therefore critical to have studies that address whether intervention based on the specific risk stratification variable or tool reduces the incidence of SCD. In this regard, ICD trials that demonstrate an improved survival rate do represent an important confirmation that the selection process provides some degree of risk stratification for SCD due to VT or VF,

because the ICD is a specific intervention designed to reduce SCD. However, the demonstration that the ICD is effective with a particular risk stratification strategy does not validate the strategy as ideal or optimal.

The applicability of current noninvasive risk stratification techniques will be discussed below, organized according to the type of testing required to obtain the information, for example, short-term ECG recordings, long-term ECG recordings, and exercise. A summary is provided in the Table.

Relation of Test Approaches to the Pathophysiology of SCD

Noninvasive approaches have been developed to detect the presence of arrhythmogenic factors that initiate and maintain VT or VF in patients with ischemic and nonischemic heart disease. The conditions that lead to VT/VF may occur transiently or may develop during the course of healing from injury to ventricular myocardium and then persist. Factors known to trigger or modulate VT/VF include changes in autonomic nervous system activity, metabolic disturbances, myocardial ischemia, electrolyte abnormalities, acute volume and/or pressure overload of the ventricles, ion channel abnormalities, and proarrhythmic actions of cardiac and noncardiac drugs. Death of myocardial cells due to ischemia, toxins, infectious agents, or chronic pressure/volume overload leads to scar formation, alterations in chamber geometry, and electrical and anatomic remodeling. The electrophysiological alterations induced by these conditions initiate and maintain VT/VF, most likely via a reentrant mechanism, although abnormal automaticity, triggered activity, or combinations of these mechanisms may be operative. The spectrum of noninvasive methods reviewed in the sections that follow were developed to detect the presence of factors known to serve as substrate or triggers of VT/VF or abnormalities in ventricular conduction and repolarization that are critical to reentry.

The specific techniques discussed are those that detect 1) slowed conduction (QRS duration, signal-averaged electrocardiogram [SAECG]), 2) heterogeneities in ventricular repolarization (QT interval, QT dispersion, T-wave alternans), 3) imbalance in autonomic tone (heart rate variability [HRV], heart rate turbulence, heart rate recovery after exercise, baroreceptor sensitivity), 4) extent of myocardial damage and scar formation (left ventricular ejection fraction [LVEF], 6-minute walk), and 5) ventricular ectopy (long-term ambulatory monitoring). Although many studies have explored the value of these techniques, the precise relationship between the presence of these abnormalities, some of which are persistently present, and the unpredictable occurrence of VT/VF has not been elucidated. Even abnormalities in combinations of these techniques may fail to detect the precise pathophysiological abnormalities that precipitate VT or VF. The limitations of these techniques, as described in this document, may therefore be due in part to our inadequate understanding of the milieu responsible for initiating clinical episodes of VT or VF. Thus, the science of risk stratification will be enhanced by further research to elucidate the structural, electrophysiological, autonomic, genetic, and proteomic milieu that precipitates SCD.

Table. Summary of Noninvasive Risk-Stratification Techniques for Identifying Patients With Coronary Artery Disease Who Are At Risk for Sudden Cardiac Death (SCD)

Technique	Conclusion
Left ventricular ejection fraction (LVEF)	Low LVEF is a well-demonstrated risk factor for SCD. Although low LVEF has been effectively used to select high-risk patients for application of therapy to prevent sudden arrhythmic death, LVEF has limited sensitivity: the majority of SCDs occur in patients with more preserved LVEF.
Electrocardiogram (ECG)	
QRS duration	Most retrospective analyses show increased QRS duration is likely a risk factor for SCD. Clinical utility to guide selection of therapy has not been tested.
QT interval and QT dispersion	Some retrospective analyses data show that abnormalities in cardiac repolarization are risk factors for SCD. Clinical utility to guide selection of therapy has not yet been tested.
Signal-averaged ECG (SAECG)	An abnormal SAECG is likely a risk factor for SCD, based predominantly on prospective analyses. Clinical utility to guide selection of therapy has been tested, but not yet demonstrated.
Short-term heart rate variability (HRV)	Limited data link impaired short-term HRV to increased risk for SCD. Clinical utility to guide selection of therapy has not yet been tested.
Long-term ambulatory ECG recording (Holter)	
Ventricular ectopy and NSVT	The presence of ventricular arrhythmias (VPBs, NSVT) on Holter monitoring is a well-demonstrated risk factor for SCD. In some populations, the presence of NSVT has been effectively used to select high-risk patients for application of therapy to prevent sudden arrhythmic death. This may also have limited sensitivity.
Long-term HRV	Low HRV is a risk factor for mortality, but likely is not specific for SCD. Clinical utility to guide selection of therapy has been tested, but not demonstrated.
Heart rate turbulence	Emerging data show that abnormal heart rate turbulence is a likely risk factor for SCD. Clinical utility to guide selection of therapy has been tested, but not yet demonstrated.
Exercise test/functional status	
Exercise capacity and NYHA class	Increasing severity of heart failure is a likely risk factor for SCD, although it may be more predictive of risk for progressive pump failure. Clinical utility to guide selection of therapy has not yet been tested.
Heart rate recovery and recovery ventricular ectopy	Limited data show that low heart rate recovery and ventricular ectopy during recovery are risk factors for SCD. Clinical utility to guide selection of therapy has not yet been tested.
T-wave alternans	A moderate amount of prospective data suggests that abnormal T-wave alternans is a risk factor for SCD. Clinical utility to guide selection of therapy has been evaluated, but the results to date are inconsistent.
Baroreceptor sensitivity (BRS)	A moderate amount of data suggests that low BRS is a risk factor for SCD. Clinical utility to guide selection of therapy has not yet been tested.

Left Ventricular Ejection Fraction

LVEF is the most widely used measure of left ventricular systolic function. As evaluated by radionuclide or radiographic contrast ventriculography or by 2-dimensional echocardiography, LVEF offers several distinct advantages over many other risk stratification measures in terms of accessibility by a large number of patients and the ease of measurement and interpretation by physicians. The accuracy of LVEF assessment is approximately $\pm 2\%$ to 6% for radionuclide angiography (6) and in excess of $\pm 10\%$ for both visual estimation and calculation by Simpson's rule with echocardiography (7). Reduced LVEF has been the most consistently reported risk factor for overall mortality and SCD in the heart failure population.

The relationship between left ventricular systolic dysfunction and death due to progressive heart failure and ventricular arrhythmias in patients who have had an MI is well estab-

lished. Studies dating back to the advent of cardiac imaging were the first to observe the association between reduced LVEF and outcome, with the majority of studies concluding that LVEF $\leq 40\%$ serves as the threshold for identifying high-risk individuals (8–10). The prognostic value of impaired left ventricular function for overall mortality and SCD has persisted despite progress in treatments for acute MI, including thrombolytic and β -blocker therapies (11–13). An analysis of 20 studies that enrolled 7294 postinfarction patients found that an LVEF $\leq 30\%$ to 40% was associated with a relative risk of 4.3 for major arrhythmic events, with a sensitivity and specificity of 59.1% and 77.8%, respectively (14). Despite these observations, however, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) noted that ICDs did not decrease overall mortality when implanted in selected patients (those with low HRV or elevated heart rate) with low LVEF within 40 days of an MI (15), a time period of particularly increased risk for SCD (16). Similarly, the

Coronary Artery Bypass Graft (CABG)-Patch trial (17) also noted no benefit of ICD therapy in a select group of patients (those with a positive SAECG) with low LVEF undergoing coronary artery bypass surgery. These data suggest that a low LVEF may be as much a marker for death due to progressive pump failure as it is for death due to SCD. Alternatively, the dynamic nature of the healing infarction may provide a substrate for which an ICD intervention is less likely to provide benefit.

Remote prior MI may result in both reduced LVEF and abnormalities of conduction and refractoriness that serve as the substrate for ventricular tachyarrhythmias. The association between left ventricular dysfunction due to coronary artery disease and SCD has been examined extensively in cohort studies and randomized, controlled trials that evaluated medical therapies and ICDs. Lower LVEF has consistently been demonstrated to be the strongest independent predictor of SCD. Further supportive evidence exists in the form of ICD trials that used LVEF either alone or in conjunction with other risk stratification methods in the inclusion criteria. The Multicenter Automatic Defibrillator Trial (MADIT) demonstrated that ICDs reduced mortality by nearly half compared with medical therapy alone in patients with class I to III heart failure, LVEF $\leq 35\%$ with nonsustained VT (NSVT), and nonsuppressible (by procainamide) ventricular tachyarrhythmia on electrophysiological study (18). Subsequent analysis of the MADIT data demonstrated that the benefit of ICD therapy was greatest in patients with LVEF $< 26\%$, especially when other risk factors were present (19). Likewise, the Multicenter Unsustained Tachycardia Trial (MUSTT), which enrolled patients with LVEF $\leq 40\%$, noted that total mortality and arrhythmic deaths/cardiac arrests occurred more frequently in patients with an LVEF $< 30\%$ (20). MADIT-II randomized patients with prior MI and LVEF $\leq 30\%$ to medical therapy or ICD implantation and demonstrated a significant 31% reduction in the risk of death with ICD implantation (21). Finally, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) randomized 2521 patients with class II or III congestive heart failure and LVEF $\leq 35\%$ due to ischemic and nonischemic cardiomyopathy and demonstrated a significant 23% reduction in mortality in ICD recipients compared with patients treated with medical therapy (22). Because ICDs only have an impact on arrhythmic death, the improvement in overall mortality seen in these trials is strong evidence of the high attributable risk of death due to arrhythmias in patients with moderate to severe left ventricular systolic dysfunction. These trials included patients with a range of New York Heart Association (NYHA) heart failure classes; the independent effects of NYHA heart failure class on risk are discussed below. Although overall risk is higher in patients with LVEF $< 35\%$ to 40% , the absolute number of SCDs is greater in patients with more preserved LVEF. This epidemiological paradox occurs because the latter subgroup is much larger than the subgroup of patients with LVEF $< 35\%$ to 40% .

In patients with nonischemic dilated cardiomyopathy, overall mortality has also been associated with LVEF (23), although few studies addressed the relationship between LVEF and SCD directly. Prospective observational studies on patients with nonischemic cardiomyopathy found that

LVEF was the only significant predictor of major arrhythmic events on multivariate analyses. The combination of low LVEF ($< 30\%$) and NSVT on Holter monitoring identified the highest-risk subgroup with a relative risk 8.2-fold that of patients with LVEF $\geq 30\%$ without NSVT (24). The SCD-HeFT and Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trials reported an annual rate of SCD lower than that seen previously in cohort studies, likely as a result of high compliance rates with appropriate medical therapies. These studies demonstrated a trend toward reduced mortality rates in patients who received ICDs (22,25).

Conclusions

There are abundant data supporting the use of LVEF to risk-stratify patients with ischemic and nonischemic cardiomyopathies. There are clinical scenarios, such as the immediate post-MI period, in which other causes of mortality may confound the use of LVEF as a specific predictor of SCD. Although low LVEF identifies a group with relatively increased risk, the majority of SCDs occur in patients with more preserved LVEF, which highlights the limited sensitivity of this technique.

Electrocardiogram

QRS Duration

QRS duration is a simple measure of the duration of ventricular activation measured on the 12-lead electrocardiogram (ECG) and is a manifestation of intraventricular or interventricular conduction delay or block. It is highly reproducible, with a coefficient of variation $< 5\%$ (26). In a broad sample of patients receiving an ECG at the VA Palo Alto Health Care System in Palo Alto, Calif, 801 (1.8%) of 44 280 had a QRS duration > 120 ms, and an additional 2300 had either right or left bundle-branch block (27). Estimates of the prevalence of QRS prolongation in the population with chronic congestive heart failure range between 20% and 50% (28), consistent with the notion that QRS prolongation becomes more prevalent in patients with advancing heart disease. Observational studies suggest that QRS prolongation is a significant marker for poor outcome in patients with depressed LVEF, especially due to coronary artery disease (29). QRS prolongation could be simply a surrogate marker for more advanced myocardial disease, but it may also contribute directly to increased mortality, because dyssynchronous ventricular activation may cause depression of cardiac function (30). It has also been suggested that slow conduction and the associated increase in dispersion of ventricular recovery directly promote ventricular arrhythmias (31,32). The Coronary Artery Surgery Study registry found that patients with bundle-branch block had more extensive coronary artery disease, a lower mean LVEF, and higher 2-year mortality than those with normal QRS duration. Furthermore, the presence of left bundle-branch block was an independent predictor of cardiovascular mortality due to SCD (33). In an unselected population with congestive heart failure, investigators found a linear association between QRS duration and the prevalence of systolic dysfunction, although no independent association between

QRS duration and all-cause mortality was recognized after adjustment for covariates (34). In contrast, the Italian Network on Congestive Heart Failure also examined the role of left bundle-branch block and found a higher prevalence of advanced heart failure and a 35% increased risk of SCD at 1 year (35). Similarly, a retrospective analysis of 669 patients with congestive heart failure of varying causes found that QRS duration ≥ 120 ms was independently associated with an increase in all-cause mortality and SCD, especially in patients with LVEF $\leq 30\%$ (36).

Subgroup analyses of randomized, controlled ICD trials in patients at increased risk for SCD have also examined the role of QRS prolongation as a predictor of overall mortality and arrhythmic death. MADIT-II found no significant differences in the effect of ICD therapy on overall mortality or mortality due to SCD in subgroup analyses stratified according to QRS duration or the presence or absence of left bundle-branch block (37). Independent analysis of the MADIT-II data by the Centers for Medicare and Medicaid Services concluded that a QRS duration > 120 ms was, in fact, an important indicator of which patients were likely to benefit from ICD therapy (38). Similarly, subgroup analysis from MUSTT concluded that patients with intraventricular conduction delay or left bundle-branch block (but not right bundle-branch block) had a 50% increase in the risk of cardiac arrest and total mortality, independent of LVEF and results of electrophysiological testing (39). Data presented from SCD-HeFT showed that the magnitude of ICD benefit depended on the definition of the cutoff point. For those patients with QRS duration ≥ 120 ms, the hazard ratio was 0.67 (95% confidence interval [CI] 0.49 to 0.93) versus a hazard ratio of 0.84 (95% CI 0.62 to 1.14) for those with QRS duration < 120 ms. In contrast, when the QRS duration cutoff was > 120 ms, the hazard ratio was 0.80 (95% CI 0.57 to 1.13) versus a hazard ratio of 0.74 (95% CI 0.46 to 0.99) for those with QRS duration ≤ 120 ms. Finally, in patients with ICDs, QRS duration has not been found to be a predictor of VT/VF that requires ICD therapy (40,41). These varied findings may reflect significant differences in the design and inclusion criteria between studies. In addition, because of the inherent limitations of subgroup analyses, any conclusions must be interpreted with caution.

The majority of cohort studies performed on patients with nonischemic dilated cardiomyopathy have not demonstrated a significant association between intraventricular conduction delay and SCD (24,42,43). ICD trials that included patients with nonischemic cardiomyopathy also evaluated the independent prognostic value of QRS width. DEFINITE did not show a relationship between QRS duration and all-cause mortality (25). SCD-HeFT, which enrolled patients with ischemic and nonischemic cardiomyopathies, reported that ICD therapy yielded a greater mortality reduction in patients with QRS duration ≥ 120 ms, but specific information on the relationship between QRS duration and mortality reduction in patients with nonischemic cardiomyopathy has not been presented (22).

Conclusions

A moderate amount of data show that increased QRS duration identifies patients at higher risk for SCD, although the data are not uniform. In the absence of prospective trials specifi-

cally designed to address this issue, the use of QRS duration to further risk-stratify patients with congestive heart failure for SCD is not recommended at this time.

QT Interval and QT Dispersion

The QT interval is a reflection of the summed ventricular action potential durations. It shortens with increasing heart rate and is commonly corrected (QTc) by Bazett's formula (QT interval divided by the square root of the R-R interval), although limitations of this correction are widely recognized. The normal corrected QT interval is slightly shorter in men than in women. The measured QT interval is influenced by the leads available for analysis and QRS prolongation, which makes assessment of the relative significance of QT prolongation alone problematic in many studies. QT-interval measurements have been shown to be highly reproducible (44), but the need for rate correction with suboptimal formulas limits the comparability of QT data in populations. QT prolongation has been associated with mortality in some observational studies in patients with depressed left ventricular function (45) but not in others (46,47). Although a relation of QT interval to overall cardiovascular risk is demonstrable in large populations (48,49), studies evaluating the QT interval for prediction of SCD risk in individuals who do not have long-QT syndrome have demonstrated mixed results but generally link prolonged QT intervals with increased risk (50). Interobserver and intraobserver variability reduce the reproducibility for QT-interval measurement, as well as QT dispersion.

QT dispersion (the maximal difference between QT intervals in the surface ECG) was postulated to reflect dispersion of myocardial recovery and to be associated with arrhythmia risk. It has been associated with increased mortality in some observational studies (45,51,52). Several recent studies have found no relation between QT dispersion and outcome (24,46,53–55). Lack of a clear physiological correlate further clouds the utility of this parameter.

Dynamic changes in QT interval during a recording period have been suggested as a marker of repolarization instability that might be linked to arrhythmia susceptibility (56–60). The QT/R-R-interval relationship for an individual patient is highly stable over time (61). A steep slope of the relation between QT interval and preceding R-R interval has been associated with SCD and mortality in initial observational studies (56,57). In a substudy of 476 patients who received ICDs for primary prevention of SCD in MADIT-II, increased QT variability was associated with an increase in spontaneous VT or VF, but 22% of patients in the lowest quartile for QT variability also experienced arrhythmias, which suggests a poor negative predictive value (59).

Conclusions

Some data exist that link abnormalities in cardiac repolarization with an increased risk for SCD. The present data do not support the use of QT interval, QT dispersion, or QT-interval variability for risk stratification for SCD in patients without the long-QT syndrome. Further studies are needed to establish whether there is clinical utility of these parameters for risk stratification.

Signal-Averaged ECG

In patients with VT, delayed or prolonged activation of small portions of the ventricle are common in regions of infarction or scar. Most infarctions do not result in complete transmural necrosis. The amount of surviving myocardium varies, as does its location. The increased separation of myocardial bundles and the disruption of their parallel orientation by fibrosis slows ventricular activation (62). During sinus rhythm, delayed ventricular activation, often extending beyond the end of the QRS complex, is more profound and is detectable at more cardiac sites in patients with sustained VT rather than in those without VT (63). Late potentials refer to low-amplitude signals that occur after the end of the QRS complex. Late potentials have been recorded in dogs with experimental infarction and correspond in time with fragmented and delayed electrograms recorded from the epicardium (64). In patients, late potentials have been correlated with late fragmented electrograms recorded directly from the heart and are related to the total mass of slowly activated tissue (63). Late potentials have been thought to represent a substrate for reentry and have been correlated in some studies (65), but not in others (66), with the site of earliest activation during VT.

Signal averaging to reduce noise allows high gain amplification and filtering to expose these signals on the surface ECG. Three time-domain measures of late potentials are commonly assessed for evidence of late potentials: QRS duration, low-amplitude signal duration, and root mean square voltage of the terminal 40 ms of the QRS. Delayed activation of the ventricle by bundle-branch block can obscure detection of late potentials, and these patients have been excluded from some analyses (67–71). Prolonged filtered QRS duration (>114 to 120 ms) appears to be the most robust measure correlated with outcome (70,72–74). Low-amplitude signal duration and root mean square measures were not associated with arrhythmic events in a large post-MI study (70). The SAECG is moderately reproducible (75), although its reproducibility is impaired by the presence of late potentials and low residual noise (76). The SAECG is either not useful or less useful in patients with right and left bundle-branch blocks.

Low-amplitude signals from regions of scar may also be obscured if the abnormal region is depolarized during the QRS. Analysis of transmural ventricular activation during sustained VTs from patients with healed infarction has confirmed that reentrant circuits involve intramural pathways located at the infarct border zone, with delayed conduction in the midmyocardium or subendocardium constituting a critical part of the circuit (77). Analysis of sinus beats from these patients demonstrated that activation of the myocardium that composed the reentrant circuit began shortly after the onset of the QRS complex and contributed little to the terminal QRS complex or ST segment. Instead, late potentials detected in SAECGs from these patients correlated with the region of myocardium activated last, which was both spatially and temporally remote from that responsible for VT in some patients (78). Frequency analysis and analysis of spectral turbulence of the SAECG may expose the presence of abnormal activity that is not dependent on the timing of

depolarization of abnormal regions, but these analyses are more involved and may be less reproducible (79–85).

The SAECG has been evaluated early after acute MI (12,71,79,86–91). Because the SAECG appears to be linked to the substrate of the underlying infarction, it would be expected that therapies that alter the substrate or its development will alter the SAECG and perhaps the risk of SCD. Thus, thrombolytic therapy reduces the incidence of an abnormal SAECG in MI survivors (91–94). SAECG performed early after MI is abnormal in 15% to 35% of patients. SCD or cardiac arrest occurs in 3.3% to 9% of these patients over the following 1 to 3 years (12,14,70,71,79). For the prediction of SCD or arrhythmic events, the sensitivity of an abnormal SAECG has been reported to vary from 30% to 76% and the specificity from 63% to 96%. The relatively low rate of events, however, results in a low positive predictive value for SCD, ranging from 7% to 40% (7% and 17%, respectively, in the 2 largest studies [14]). The negative predictive value is high, exceeding 95%, but this is also related to the low event rate.

Prolonged QRS duration on SAECG is associated with increased mortality and increased risk of arrhythmic events (95–97). The MUSTT investigators assessed the relation of the SAECG to arrhythmic events in 1268 patients with LVEF <40% and NSVT who did not have bundle-branch block (96). Recent acute MI had occurred in 15% of the subjects. A prolonged filtered QRS >114 ms was associated with a 28% risk of arrhythmic events during 5 years of follow-up compared with a 17% risk of events for those with shorter filtered QRS durations (hazard ratio 1.90, 95% CI 1.46 to 2.46). Prolonged QRS duration was also associated with inducible sustained monomorphic VT or polymorphic VT induced by 2 extrastimuli, with a sensitivity of 46%, specificity of 57%, positive predictive value of 42%, and negative predictive value of 62%.

The strategy of placing an ICD in patients with a positive SAECG was tested in the CABG-Patch study, which enrolled patients with LVEF <36% who had an abnormal SAECG and were undergoing coronary artery bypass surgery. At the time of surgery, patients were randomized to receive or not receive an ICD. ICD therapy did not improve survival, although arrhythmic deaths were reduced (17,98). Revascularization may have reduced the risk of SCD, or the criteria of a low LVEF and a positive SAECG may not have resulted in the selection of a group that was at sufficiently high risk when bypass surgery was being performed. In a series of 561 patients undergoing coronary artery bypass surgery, 72% of whom had preserved ventricular function, the postoperative SAECG was abnormal in 27% of patients, but this was not related to outcome (99).

In patients with nonischemic dilated cardiomyopathy, evidence of late potentials detected by SAECG has been associated with a history of ventricular arrhythmias (100–102). SAECG has predicted SCD and total mortality in some studies (103) but not in others, including 3 relatively large series of 137, 202, and 343 patients, respectively (24,104–109). Some studies have found that an abnormal SAECG predicted death due to progressive heart failure rather than SCD (110,111).

Conclusions

Abundant data show that an abnormal SAECG may identify patients with prior MI at risk for SCD. Given the high negative predictive value of this test, it may be useful for the identification of patients at low risk. Routine use of the SAECG to identify patients at high risk for SCD is not adequately supported at this time. Further studies are required to assess the utility of this test.

Short-Term HRV

Analysis of HRV provides a means of assessing autonomic nervous system modulation of the sinus node to infer autonomic activity on the rest of the heart, particularly the ventricles. Although the contributions of sympathetic and parasympathetic tone may be difficult to dissect in individual circumstances, studies using autonomic blockade have demonstrated that HRV is almost completely due to autonomic input to the sinus node. HRV then provides a surrogate for the autonomic effects in the ventricle that are postulated to be important in the pathogenesis of VT and VF. Cardiac arrhythmias are often initiated by or occur in patients with enhanced sympathetic and diminished parasympathetic tone. Thus, it has been proposed that an analysis of HRV, particularly its parasympathetic effects on the sinus node, can potentially predict mortality. Spectral analysis of heart rate identifies periodic oscillations in rate that are high-frequency (0.15 to 0.45 Hz) and low-frequency (0.04 to 0.15 Hz) ranges (112). Respiratory sinus arrhythmia mediated by fluctuations in parasympathetic tone is a major determinant of the high-frequency component. Sympathetic nervous activity contributes importantly to low-frequency HRV. Other factors are also involved, and the genesis of HRV in health and disease is not completely understood. The relative roles of heart rate and HRV as indicators of autonomic activity and prognosis continue to be debated (113,114). Although short-term HRV has moderate reproducibility in normal subjects, it is less reproducible in patients with congestive heart failure (115). Furthermore, there is marked interindividual variation in the relationship of short-term HRV to parasympathetic effect (116). Thus, the identification of clear limits for the differentiation of normal and abnormal results in an individual may be difficult.

In a 900-subject cohort of adults, those in the lowest tertile for HRV assessed from 2-minute ECG recordings had an increased risk of cardiovascular death (117). A small study of patients evaluated early after MI did not find a relation of short-term HRV to arrhythmic events, possibly owing to sample size (118). In patients with chronic heart failure, La Rovere and coworkers (119) analyzed 8-minute recordings during quiet rest with spontaneous breathing or controlled breathing. A diminished ratio of low- to high-frequency power during spontaneous breathing, a standard deviation of R-R intervals <15 ms, and diminished low-frequency power during controlled breathing were univariate predictors of arrhythmic mortality. In multivariate analysis, diminished low-frequency power during controlled breathing was associated with a 5-fold increase in arrhythmic mortality. The combination of preserved low-frequency power and fewer than 86 ventricular premature beats (VPBs) per hour was

associated with a 3% SCD risk compared with 23% for the remainder of the population.

Conclusions

Limited data link impaired short-term HRV to sudden death. At the present time, its use for risk stratification for SCD is not recommended.

Long-Term Ambulatory ECG Recording (Holter)

The ambulatory ECG (AECG) or Holter monitor has been available for decades, and the clinical utility of the device has expanded and changed over the years. This section addresses quantification of ventricular arrhythmias (VPBs and NSVT) and HRV/heart rate turbulence recorded by the AECG as a tool for assessing risk for SCD. This is drawn in part from the American College of Cardiology/American Heart Association guidelines for ambulatory electrocardiography (120).

Ventricular Ectopy and NSVT

Although the AECG can reliably record the presence of VPBs and NSVT, the day-to-day reproducibility of the frequency of these arrhythmias is poor (120). In the 1970s and 1980s, observational studies demonstrated that VPBs (generally 10 or more VPBs per hour) and NSVT as recorded by an AECG in post-MI patients were risk factors for subsequent mortality (8,10,121,122). Data suggest that ectopy beyond 10 VPBs per hour does not convey a further increase in risk (123). It has also been suggested that VPBs are an independent predictor of mortality, whereas NSVT may not be a predictor (124). The initial studies described patients without reperfusion, but a similar relationship has been observed (although with somewhat reduced risk) in the era of thrombolysis and acute reperfusion (13,123,125–127). In the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico 2 (GISSI-2) study (127), mortality was 5.5% at 6 months for patients with >10 VPBs per hour compared with 2% in those with less frequent ectopy. The positive predictive value of ventricular ectopy after MI for predicting cardiac arrhythmic events or death generally ranges from 5% to 15%, with a negative predictive value of 90% or more (120). When combined with reduction of LVEF, ventricular ectopy becomes a stronger risk factor for mortality. In the European Myocardial Infarction Amiodarone Trial (EMIAT), among postinfarction patients with LVEF ≤40%, mortality was higher in patients with frequent or complex arrhythmias on AECG than in those without (20% versus 10%) (128).

Patients with nonischemic cardiomyopathy are at increased risk of SCD and frequently have high-grade ventricular ectopy and NSVT (129,130); however, the relationship between arrhythmias on AECG and cardiac arrest is much less clear than in the case of ischemic cardiomyopathy (120). Observational trials make up the majority of data available, and NSVT is used more commonly than ventricular ectopy for risk stratification, likely in relation to the high frequency of VPBs in this population. The Gruppo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial, which included a majority of patients with nonischemic cardiomyopathy, confirmed the prevalence of ventricular

arrhythmias on AECG in patients with heart failure and LVEF $\leq 35\%$ (131). NSVT was an independent predictor of mortality, but ventricular couplets appeared to be equally predictive (132). Couplets and/or NSVT were detected in 62.7% of the study population, with a 50.8% mortality rate. The remaining 37.3%, without couplets or NSVT, had a lower mortality rate of 26.3%.

The sensitivity of NSVT in relationship to SCD or total death varies among several studies, ranging from 31% to 71% (120,122,129,130,133–135). The positive predictive value is low, ranging from 20% to 50%, although the negative predictive value has been cited as 72% to 93%.

There is a long history of intervention trials designed to reduce mortality in high-risk patients with VPBs or NSVT. The Cardiac Arrhythmia Suppression Trial (CAST) was a groundbreaking, double-blind, randomized study that demonstrated that suppression of ectopy and nonsustained VT after MI with type IC antiarrhythmic drug therapy actually increased mortality in this population (136). CAST demonstrated that markers of risk are not necessarily appropriate targets for therapeutic interventions. Randomized, controlled trials have used NSVT, often documented by AECG, to identify patients who should undergo electrophysiological testing and further treatment if VT was inducible (18,137). These studies showed significant 50% to 60% reductions in mortality in the ICD-treated groups, but intervention was based on electrophysiological testing.

In patients with nonischemic cardiomyopathy and congestive heart failure, LVEF $\leq 35\%$, and ventricular arrhythmias (NSVT or an average of 10 or more VPBs per hour), DEFINITE demonstrated a trend toward improvement in overall survival (hazard ratio 0.65, 95% CI 0.40 to 1.06, $P=0.08$) and a reduction in arrhythmic events (hazard ratio 0.20, 95% CI 0.06 to 0.71, $P=0.006$) with ICD therapy. The mortality rate of the non-ICD group was 7% per year, but no comparison group of patients without ventricular arrhythmias was reported.

Conclusions

There is abundant information linking the detection of ventricular arrhythmias (VPBs, NSVT) on AECG in post-MI patients with left ventricular dysfunction for risk assessment for sudden death. Use of the AECG in this setting has been classified as a class IIb recommendation (120); however, the incremental risk stratification provided by this finding in patients with LVEF $\leq 35\%$ is unclear (22). On the other hand, patients with LVEF between 35% and 40% (137) may warrant AECG recording to assess for NSVT, because this group has been shown to benefit from an ICD if VT is induced at electrophysiological study. Patients with preserved left ventricular function after MI are generally at low risk, and current data suggest that they would not benefit from undergoing risk stratification with AECG recording. Finally, in patients with dilated cardiomyopathy, DEFINITE (25) required the presence of ventricular ectopy or NSVT on AECG, whereas SCD-HeFT (22) did not; thus, the utility of AECG for risk stratification in this population remains unclear.

Long-Term HRV

Three groups of techniques have been used to quantitatively examine HRV from long-term AECG recordings and address

its ability to supply prognostic information in patients with underlying cardiac disease; these have been summarized in a joint European Society of Cardiology/North American Society for Pacing and Electrophysiology report published in 1996 (112). The time- and frequency-domain indices have been evaluated extensively. Power spectral analysis has focused on several different frequency bands (138): ultralow frequency, very low frequency, low frequency, and high frequency, with power expressed in absolute or normalized units. There remains debate about which factors alter HRV in each of the frequency bands. Assessment of long-term HRV from 24-hour AECG recordings is influenced by circadian rhythms and patient activity (139). Thus, because of the changing autonomic control or modulation of the heart rate throughout the day, the high- and low-frequency power components are not stationary, and their link to specific physiology is therefore less well defined. Analysis of these bands from short-term recordings during controlled conditions avoids these potentially confounding problems. Time- and frequency-domain analyses are simply different methods to examine the same data set. As such, it is not surprising that a high degree of correlation exists among parameters (140). There are data to support the reproducibility of these measures (112). More recently, nonlinear methods have also been used to examine HRV. These studies are much less well developed than studies of time- and frequency-domain analysis. Of the nonlinear techniques that are available, the largest amount of clinical data is available for the power-law relationship. To derive the power-law relationship, the frequency-domain data are plotted [$\log(\text{power})$ versus $\log(\text{frequency})$], and the inverse slope of this plot helps to define the complexity of heart rate fluctuations. The complexity of variability analyzed by nonlinear methods can also be expressed with fractal scaling or fractal dimension.

The ability of HRV to predict arrhythmic, cardiac, or total mortality has been studied in a variety of different populations. In 1987, Kleiger et al (141) reported a relative risk of 5 for all-cause mortality in patients with low time-domain measures of HRV. Since then, a number of studies have reported an increased mortality in patients with low time- and frequency-domain measures of HRV. The ability of frequency-domain measures to predict mortality appears approximately equivalent to that of time-domain measures. In most studies, patients with angina or heart failure and those who had experienced an MI had a higher mortality if HRV was low. In general, the relative risk is in the range of 2 to 3, but lower numbers have been obtained in large population studies, such as the Framingham study. In different studies, different time and frequency measures have shown the highest predictive value for all-cause mortality or sudden death. Overall, HRV was a better predictor of total mortality than of SCD mortality (117,119,140,142,143). Of nonlinear methods, the power-law relationship has been studied the most extensively. Huikuri et al (144) examined a “random sample” of 347 subjects who were >65 years old. In that study, the nonlinear power-law relationship was the best predictor of all-cause mortality (relative risk=7.9, $P<0.001$); however, in a multivariate analysis, the relative risk decreased to 1.74. Time-domain measures did not perform as well in their analysis. Huikuri et al (145) also examined

short-term fractal scaling (α) in a different patient population and found it had a better predictive value than time-domain measures; however, more large-scale population studies will be required before there are adequate data to determine whether this methodology holds promise for risk stratification.

In most population studies using multivariate analysis, HRV provides significant, independent prognostic information. The Autonomic Tone and Reflexes After MI (ATRAMI) study (146) showed that after MI, patients with low HRV had a relative mortality risk of 3.2, with accounting for LVEF and ventricular ectopy. Two recent intervention trials used HRV to risk-stratify patients. In DINAMIT (15), 675 post-MI patients who had decreased LVEF and low HRV (or elevated heart rate) were randomized to receive or not receive an ICD. There was no significant difference in survival between the groups. The ICD reduced arrhythmic mortality, but nonarrhythmic mortality increased in the patients who received an ICD. It was believed that low HRV in this patient population was an indicator of more advanced hemodynamic disease, and patients in the ICD group who received appropriate shocks ultimately died of congestive heart failure. A second trial used HRV analysis to divide patients into low- and high-risk groups. Camm *et al* (147) studied 3717 post-MI patients with left ventricular dysfunction and characterized them into low- and high-risk groups on the basis of the triangular index of HRV. Although the trial was designed to examine the effects of an antiarrhythmic drug (azimilide) on survival, data on the prognostic importance of HRV were also reported. By multivariate analysis, low HRV increased risk of all-cause mortality with a hazard ratio of 1.46 (95% CI 1.1 to 1.94); however, low HRV did not predict arrhythmic mortality. In the Marburg Cardiomyopathy Study (24), of the 263 patients with nonischemic dilated cardiomyopathy who were in sinus rhythm, low HRV was not a multivariate predictor of transplant-free survival or of arrhythmic events.

Conclusions

Abundant data show that depressed HRV is a predictor of total mortality. Despite the theoretical pathophysiological link among abnormal HRV, autonomic tone, and arrhythmogenesis, the present data show that HRV may be a better marker of nonarrhythmic mortality. Further studies are needed to establish whether HRV has a role in risk stratification for SCD.

Heart Rate Turbulence

Heart rate turbulence describes the short-term fluctuation in sinus cycle length that follows a VPB (148). Although the mechanism of heart rate turbulence is not known with certainty, it has been postulated that it measures vagal responsiveness in a fashion similar to baroreflex sensitivity (BRS). After a premature beat and a compensatory pause, there is a typical increase in blood pressure due to the prolonged filling in the cycle of the compensatory pause. Reflex parasympathetic activation ensues and slows the heart rate. This parasympathetic reactivation can be defined by the time of onset of the return of the heart rate to normal and the slope (turbulence slope) of that return. Heart rate turbulence requires the response to a number of premature beats (15 to

20) to be averaged. As with other techniques that purport to measure the effects of autonomic tone on the sinus node, a higher slope, which indicates more parasympathetic responsiveness, should correlate with improved prognosis. Heart rate turbulence has been examined primarily in post-MI patients (148–150). The relative risk imparted by low heart rate turbulence in patients who have had an MI appears impressive. For example, in an ATRAMI substudy (151), there was a relative risk of ≈ 4 in multivariate analysis. A composite autonomic index, which included BRS and time-domain measures of HRV, increased the relative risk to 8. A smaller number of studies of patients with nonischemic dilated cardiomyopathy, chronic congestive heart failure, or hypertrophic cardiomyopathy (HCM) and patients undergoing revascularization have also suggested a predictive value of heart rate turbulence (24,149,151–154). In the Marburg Cardiomyopathy Study of 242 patients with nonischemic dilated cardiomyopathy (155), heart rate turbulence onset was a multivariate predictor of transplant-free survival (relative risk 2.95, 95% CI 1.11 to 7.48) but not of arrhythmic events.

Heart rate turbulence is potentially attractive as a risk stratification tool because it can be performed with a relatively small number of premature beats from 24-hour AECG and does not require blood pressure monitoring or intervention, as BRS does. Further data regarding its reproducibility are needed. Although some studies suggest it has significant predictive value after MI, only a few studies have been completed. Follow-up in some studies was not long term, and intervention trials based on heart rate turbulence have not been performed.

Conclusions

Emerging data show that abnormal heart rate turbulence is associated with increased mortality. Further studies are needed to establish whether there is clinical utility of this parameter for risk stratification.

Exercise Test/Functional Status

Exercise Capacity and NYHA Class

Left ventricular dysfunction is well established as a risk factor for sudden death; however, the clinical syndrome of congestive heart failure itself can also contribute to arrhythmogenesis in patients with ventricular dysfunction and can increase mortality in patients with either an ischemic or nonischemic dilated cardiomyopathy, independent of LVEF. Heart failure is associated with many factors that predispose to ventricular arrhythmias, including increased circulating catecholamines, electrolyte imbalances caused by diuretic use, prolonged repolarization, stretch-induced afterdepolarizations, and Purkinje system conduction delay. Manifestations of neurohormonal activation, such as hyponatremia and increased plasma norepinephrine, renin, and natriuretic peptide levels, have been found to be predictive of mortality (156). Some medical therapies for congestive heart failure have been shown to reduce both progressive heart failure and SCD due to cardiovascular causes (2,157).

ICD trials have found that heart failure symptoms are associated with defibrillator therapies. A recent study, the Triggers Of Ventricular Arrhythmias (TOVA), identified

NYHA functional class III as the strongest independent predictor of appropriate ICD therapy (158). SCD-HeFT found a mortality benefit from ICD therapy for primary prevention among patients with congestive heart failure and either an ischemic or nonischemic dilated cardiomyopathy. Subgroup analysis showed that patients with class III heart failure did not appear to benefit compared with patients with class II heart failure (22). On the other hand, DEFINITE, which enrolled only patients with a nonischemic cardiomyopathy, found a greater benefit of ICD therapy among patients with class III heart failure than among patients with class II heart failure (25). In MADIT-II, which enrolled only post-MI patients, there were no significant differences in the beneficial effect of ICD therapy on survival in subgroup analyses stratified according to NYHA class (21).

The primary limitation of the use of heart failure severity to risk-stratify patients with systolic dysfunction for SCD is that although mortality increases with the severity of heart failure, the proportion of deaths due to SCD decreases as deaths due to progressive pump failure increase (156). The Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) showed that the overall mortality rate for patients with NYHA class II symptoms was 5% and that 85% of those deaths were sudden. In contrast, the overall mortality rate for patients with class IV symptoms was 21%, with only 33% of those being SCDs. Therefore, even if ICD therapy eliminated SCD in patients with advanced heart failure, it is not clear what the net overall impact would be on mortality.

The use of heart failure classification to identify patients with systolic dysfunction who are at risk for SCD is also limited by its subjectivity. One study found that NYHA estimates made by 2 physicians had a reproducibility of only 56% and that only 51% of the estimates agreed with treadmill exercise performance (159). Another important limitation of heart failure functional status is that patients frequently transition from 1 class to another over time. Objective measures of functional capacity, such as peak oxygen consumption with exercise and the 6-minute hall walk test, have been shown to be reliable and reproducible (160,161). Measurement of peak oxygen uptake with exercise appears to be superior to clinical variables, hemodynamics, and exercise time in predicting mortality in patients with severe chronic heart failure (162). Although measurements during exercise are more objective than NYHA classification, these tests appear to be no more specific for mode of death than functional classification (162).

Conclusions

Although the syndrome of congestive heart failure may predispose to ventricular arrhythmias and SCD in patients with systolic dysfunction, its value as a risk stratification tool is untested. Furthermore, although overall mortality increases as the severity of heart failure increases, the proportion of deaths due to sudden cardiac arrest from a treatable ventricular tachyarrhythmia decreases as more patients die of progressive pump failure.

Heart Rate Recovery and Recovery Ventricular Ectopy

Immediately after graded exercise, heart rate normally falls in a biphasic manner, with an initial rapid decline occurring

during the first 30 seconds to 1 minute of recovery (163). Imai and colleagues (163) demonstrated that this initial steep descent is marked in athletes and attenuated in patients with heart failure and that it can be eliminated by administration of atropine. Thus, parasympathetic reactivation likely plays a major role in regulating heart rate recovery. Because impaired parasympathetic tone correlates with increased risk of death, it was hypothesized that an attenuated heart rate recovery would similarly predict an increased risk of death. In a cohort study of 2428 patients who were referred for exercise myocardial perfusion imaging and who were candidates for first-time coronary angiography, a 1-minute heart rate recovery ≤ 12 beats per minute was associated with a markedly increased risk of all-cause death (positive predictive value 19%, negative predictive value 95%, confounder-adjusted hazard ratio 2.0, 95% CI 1.5 to 2.7) (164).

Subsequent investigations have confirmed the link between decreased heart rate recovery and all-cause death in a variety of groups (165). Specifically, heart rate recovery has been shown to be predictive of mortality even after accounting for the Duke treadmill exercise score (166), left ventricular systolic function (167), the type of recovery protocol used (164,167,168), and angiographic severity of coronary disease (169). Heart rate recovery predicts mortality along with exercise capacity in men with diabetes mellitus (170). Among patients with imaging evidence of ischemia, a low heart rate recovery identifies patients for whom the survival benefit of revascularization is attenuated (164); that is, patients with ischemia are most likely to realize improved survival if heart rate recovery is normal. Investigators from the Paris Civil Servants study reported a link specifically between heart rate recovery and SCD, but these subjects were all free of cardiovascular disease at the time of exercise testing (168).

Despite the strong data linking heart rate recovery to mortality, its routine use for clinical risk stratification has been brought into question (171). The ideal recovery protocol and abnormal cutoff value are unclear; some advocate an upright cool-down period with a cutoff value of ≤ 12 beats per minute into recovery (164,166), whereas others support a sit-down recovery with a cutoff value of ≤ 22 beats per minute at 2 minutes into recovery (165). When a supine recovery is mandated, as in stress echocardiography, a cutoff value of ≤ 18 beats per minute has been described (167). In addition, the reproducibility of an abnormal result may not be sufficient to apply the test for individual (versus population) risk stratification (172). There are no substantive data in patients with dilated cardiomyopathy.

A phenomenon related to heart rate recovery is ventricular ectopy during recovery, which has also been hypothesized to reflect parasympathetic activity. Occurrence of frequent or severe ventricular ectopy during the first 5 minutes of recovery after exercise has been linked to risk of death in patients without and with heart failure and/or coronary artery disease (173,174).

Conclusion

Although heart rate recovery and ventricular ectopy during recovery are new and interesting markers of mortality, their value as risk stratification tools for SCD is untested.

T-Wave Alternans

In 1994, Rosenbaum et al (175) first related T-wave alternans to high-risk findings on electrophysiological testing and to an increased risk of serious arrhythmic events. T-wave alternans is a reflection of repolarization alternans at the level of the single cell and most likely arises when heart rate exceeds the capacity of cardiac cells to cycle intracellular calcium (176). Therefore, T-wave alternans is a rate-dependent phenomenon and tends to occur at relatively lower heart rates in patients susceptible to life-threatening ventricular arrhythmias. Interestingly, by amplifying electrical heterogeneities between neighboring cardiac cells, T-wave alternans has been directly linked to a mechanism of arrhythmogenesis (177). Detection of T-wave alternans requires graded exercise to elevate heart rate, as well as special electrodes and processing to record the microvolt-level T-wave alternans with high fidelity. Because of the need to achieve a target heart rate with regular R-R intervals, a significant percentage of tests are indeterminate owing to either failure to reach target heart rate, atrial fibrillation, or frequent ectopic activity. T-wave alternans is moderately reproducible, with concordance on repeated tests of 65% to 75% (178,179) and 80% to 90% when only patients with determinate results are considered (178,179).

A number of observational cohort studies have been published that suggest that microvolt T-wave alternans may work at least as well as electrophysiological testing for prediction of SCD or major arrhythmic events. Recent cohort studies that involved at least 100 patients found that T-wave alternans was associated with substantially increased risk and predicted events as well as or better than other markers, including LVEF, electrophysiological testing, SAECG, BRS, and HRV (97,105,180–182). Furthermore, T-wave alternans predicted risk in patients with coronary artery disease (181,183) and in patients with dilated cardiomyopathy (105). In all of these studies, patients not manifesting T-wave alternans were at low risk for SCD.

Two important methodological considerations are the type of stress used to induce T-wave alternans and the threshold for labeling a test abnormal. Although pacing-induced T-wave alternans has been linked to ventricular arrhythmia risk (182), one head-to-head comparison study found that exercise-induced T-wave alternans was a better predictor (183). The typical definition for an abnormal T-wave alternans test is the occurrence of $>1.9 \mu\text{V}$ of alternans starting at a heart rate of <110 beats per minute. Tanno and colleagues (182), in a study of pacing-induced T-wave alternans, found that increasing the heart rate cutoff can increase the negative predictive value to 100% but at the cost of a lower positive predictive value. Of note, a significant percentage of tests are indeterminate; many studies have classified these patients as nonnegative and have noted a similar prognosis as that for patients with a positive result. This may relate to the underlying factors responsible for the indeterminate test, ie, inability to achieve the necessary heart rate.

Despite the consistency of the reports linking T-wave alternans to risk, published studies are limited by the sometimes highly select patient samples, relatively low number of end points, use of composite end points (184), and lack of randomization. One recent cohort study of 177 patients with coronary artery disease and LVEF $\leq 30\%$ suggested that

T-wave alternans may be better than QRS duration for identifying patients likely to benefit from ICDs (185). The hazard ratios for 2-year mortality were 4.8 for abnormal T-wave alternans and 1.5 for prolonged QRS duration. A multicenter study (186) of 549 patients (49% with coronary artery disease) with LVEF $\leq 40\%$ who underwent T-wave alternans testing reported that the 2-year event (death or nonfatal sustained ventricular tachyarrhythmia) rate was 12.3% in the 162 patients with a positive test, 17.5% in the 198 patients with an indeterminate test, and 2.5% in the 189 patients with a negative test (hazard ratio 6.5 for an abnormal test). Event rates were significantly greater in patients with both ischemic and nonischemic heart disease who had abnormal versus normal T-wave alternans (16.8% and 13.3%, respectively, for an abnormal result versus 4.8% and 0%, respectively, for a normal result). Similarly, an observational study (187) of 768 patients with ischemic cardiomyopathy (LVEF $\leq 35\%$) found that a positive or indeterminate T-wave alternans test was associated with increased mortality risk (stratified hazard ratio 2.24, 95% CI 1.34 to 3.75) and increased risk of arrhythmic mortality (stratified hazard ratio 2.29, 95% CI 1.00 to 5.24). In contrast, in the Marburg Cardiomyopathy Study (24), T-wave alternans was neither a univariate nor a multivariate predictor of either transplant-free survival or arrhythmic events. A meta-analysis of 19 studies including 2608 patients (188) demonstrated that T-wave alternans was a strong univariate predictor of arrhythmic events in patients with ischemic heart failure (relative risk 2.42, 95% CI 1.30 to 4.50) and nonischemic heart failure (relative risk 3.67, 95% CI 1.50 to 8.96).

Although data support the use of T-wave alternans as a risk factor for SCD, the precise role of the use of this technology is unclear. The value of T-wave alternans may be enhanced when combined with other major risk predictors (181). Two large trials presented their findings at the 2006 Scientific Sessions of the American Heart Association regarding the use of T-wave alternans. The ABCD trial, which enrolled 566 patients with coronary artery disease and LVEF $\leq 40\%$, found that a positive T-wave alternans test was as predictive of arrhythmic events as a positive electrophysiology study. Importantly, the event rate for patients in whom both tests were negative was low. In contrast, a 490-patient substudy of SCD-HeFT found no significant difference in arrhythmic events between those who had a positive versus a negative T-wave alternans test. Of note, 41% of the population had an indeterminate result.

Conclusions

A moderate amount of data suggest that T-wave alternans may be useful for risk stratification for SCD. Further information will be required to determine how to implement this test in clinical practice.

Baroreceptor Sensitivity

BRS refers to the adaptation of cardiac periods (R-R intervals) to changes in blood pressure. The baroreflex mechanism has been established as a central part of the regulation of the cardiovascular system, particularly in the control of parasymp-

pathetic and sympathetic outflow to the heart and the peripheral vessels (189).

There are different methods of evaluating BRS, but the one that is most applicable to routine clinical use is probably the phenylephrine method (189). In essence, BRS is assessed by this method during a brief period of controlled blood pressure change. Most often, such a provocation is caused by the injection of an intravenous bolus of phenylephrine (an α -agonist that causes reflex parasympathetic enhancement). Precise, simultaneous recordings of the ECG-derived R-R intervals and systolic blood pressure values are necessary to calculate BRS. Specifically, BRS is expressed as the slope of the regression line showing the dependency of R-R intervals on blood pressure values. In healthy individuals, the intravenous administration of 25 to 100 μ g of phenylephrine results in a >20-mm Hg increase in systolic blood pressure, and R-R intervals are prolonged by >10 ms for each 1-mm Hg of pressure increase. Under optimal experimental conditions, BRS is only moderately reproducible, with a coefficient of variation of 38% on repeated tests (189).

Extensive experimental work convincingly demonstrated a close link between reduced BRS and increased risk for serious ventricular tachyarrhythmias (190). La Rovere et al (191) prospectively determined BRS in 78 post-MI patients who were followed up for 2 years, during which time 7 cardiovascular deaths occurred, including 4 sudden deaths. BRS was significantly lower in the 7 deceased patients than in the survivors. These results were subsequently confirmed by other studies (192,193). An important step toward establishing BRS determination for risk stratification after MI was achieved by the multicenter, prospective ATRAMI study (146). In contrast to most previous studies, ATRAMI was a prospective study evaluating the accuracy of BRS and HRV in predicting cardiac mortality. The trial used prospectively defined cutoff values for both autonomic markers. In 1284 postinfarction survivors, HRV and BRS were assessed at the time of hospital discharge. During 21 months of follow-up, there were 44 cardiac deaths and 5 nonfatal cardiac arrests. Depressed HRV (standard deviation of normal <70 ms) or BRS (<3.0 ms/mm Hg) carried a significant multivariate risk of cardiac mortality (3.2 [95% CI 1.4 to 7.4] and 2.8 [1.2 to 6.2], respectively). Risk increased further when both parameters were depressed. The association of low BRS or SDNN with a reduced LVEF (<35%) carried a relative risk of 8.7 (4.3 to 17.6) or 6.7 (3.1 to 14.6), respectively, compared with patients with better preserved LVEF and less compromised HRV or BRS. The main conclusion from this important trial is that early after acute MI, the analysis of parasympathetic reflexes yields significant prognostic value independent of LVEF or other noninvasive risk stratifiers. Analysis of BRS adds to the prognostic value of HRV, which signifies that measures of autonomic tone and parasympathetic reflex activity are not redundant but rather complementary (146).

Subsequent analyses showed that when examined in conjunction with depressed LVEF, BRS contributed in a novel way to risk stratification. Specifically, within the group of patients with LVEF <35%, those with preserved BRS had a significantly better 2-year survival than those with depressed BRS. This was even more evident for major arrhythmic events (3% versus 16%). The latter analysis must certainly be

repeated in larger patient populations. In the Marburg Cardiomyopathy Study (24), of the 263 patients with nonischemic dilated cardiomyopathy who were in sinus rhythm, BRS was not a multivariate predictor of arrhythmic events but exhibited a trend toward predicting transplant-free survival (relative risk 1.42, 95% CI 0.95 to 2.13).

Conclusions

A moderate amount of data suggest that BRS may be useful for risk stratification for SCD in patients with coronary artery disease. Further studies are needed to establish the clinical utility, if any, of this parameter for risk stratification.

Other Testing

In addition to the noninvasive testing described in detail above, there are several other tests that may be useful for risk stratification. Evaluation of myocardial ischemia is clearly important, because this may serve as an important trigger for life-threatening ventricular arrhythmias, either in patients with preexisting substrate or, less commonly, as a primary cause. Electrophysiological testing has demonstrated utility in identifying the substrate for sustained VT and could become an important part of a risk stratification strategy. Finally, newer techniques, such as characterization of infarct size or morphology by contrast-enhanced magnetic resonance imaging, could provide information on susceptibility to ventricular tachyarrhythmias in patients with coronary artery disease (194) and nonischemic dilated cardiomyopathy (195).

Hypertrophic Cardiomyopathy

Because HCM is the most common cause of SCD in the young, including competitive athletes (196), the unique risk stratification issues related to HCM are reviewed. HCM is a genetic heart disease with heterogeneous clinical expression. Although only a minority of the overall HCM population are at high risk for sudden death, strategies for risk stratification and isolation of that important subset have constituted a major investigative focus (197). It has also been appreciated (197) that the literature may have previously overestimated the risks associated with HCM, because many of the published data had been derived from tertiary referral centers with disproportionate numbers of high-risk patients.

In contrast to the ischemic and nonischemic cardiomyopathies under consideration in the present statement, the vast majority of patients with HCM at risk for SCD are young, asymptomatic (or mildly symptomatic) adolescents or adults <35 years old. These patients may not have reliable warning signs, and thus, SCD can be the initial disease presentation. However, SCD risk also extends through midlife and beyond; therefore, achieving any particular age does not itself confer immunity to sudden death.

Many of the tests or parameters described in this statement to assess risk for SCD in ischemic and nonischemic cardiomyopathies are generally not applicable to patients with HCM. These include 12-lead ECG patterns, which are usually abnormal and particularly heterogeneous in HCM, with little predictive value regarding outcome. Because HCM is characterized by hyperdynamic or normal left ventricular func-

tion, LVEF has little or no prognostic power, except in the small minority of patients in the end-stage phase with systolic dysfunction due to diffuse LV scarring. Heart rate recovery, HRV, SAECG, and T-wave alternans have not been well studied as markers of SCD risk in this disease.

Because of the relatively low prevalence of HCM in general cardiological practice, its diverse presentation and mechanisms of death, and skewed patient referral patterns, the level of evidence governing risk stratification strategies has most often been derived from nonrandomized and retrospective investigations. Furthermore, the long risk period for this relatively young patient population and the low SCD event rate represent obstacles to developing and testing risk stratification strategies. Large-scale controlled and randomized study designs, such as those that have provided important answers regarding the management of coronary artery disease and congestive heart failure, have generally not been available in HCM patients owing to these demographic factors. Additionally, most of the clinical markers of SCD risk in HCM are limited by relatively low positive predictive value ($\leq 20\%$), largely due to low event rates. However, high negative predictive values attributable to these markers ($\approx 90\%$) suggest that the absence of risk factors may be used to develop a profile of those patients with low likelihood of sudden death.

The highest risk for SCD (197–200) has been associated with 1) prior cardiac arrest or spontaneously occurring sustained VT; 2) family history of a premature HCM-related death, particularly if SCD occurred in a close relative, or when multiple; 3) unexplained syncope, particularly in young patients; 4) NSVT (usually asymptomatic short bursts of 3 to 6 beats at ≥ 120 bpm) on long-term AECG recordings, particularly if prolonged or multiple/repetitive on serial studies; 5) attenuated or hypotensive blood pressure response during upright exercise, indicative of hemodynamic instability; and 6) extreme left ventricular hypertrophy with maximum wall thickness ≥ 30 mm on 2-dimensional echocardiography, particularly in adolescents and young adults.

Available data suggest that left ventricular outflow obstruction (gradient ≥ 30 mm Hg at rest) assessed by continuous-wave Doppler echocardiography can only be regarded as a minor risk factor for SCD in HCM (positive predictive value of only 7%) (201). Myocardial ischemia (associated with impaired coronary vasodilator capacity), in the absence of coronary artery disease, is probably an important pathophysiological mechanism in HCM, as a consequence of abnormal microvasculature (ie, intramural “small-vessel disease”). However, ischemia (or its consequences) as a prognostic marker in HCM has proved to be difficult to assess with standard exercise testing, thallium imaging, echocardiography, or magnetic resonance imaging. Positron electron tomography has shown a significant relationship between myocardial ischemia and the progression of heart failure in HCM, but not specifically with sudden death. It has also been proposed, on the basis of genotype-phenotype correlations in a relatively small number of families, that the genetic defects responsible for HCM could represent the primary determinant of SCD risk, with specific mutations conveying either favorable or adverse prognosis. However, the clinical utility of genetic testing for predicting prognosis and developing individual patient management strategies is uncertain.

Although the available data on risk stratification for SCD are substantial, it is important to underscore that precise criteria for identification of high-risk patients by clinical risk markers are not complete. Although it has been possible to identify many such patients only by history taking or noninvasive testing, a minority of HCM patients who die suddenly are without any of the currently acknowledged risk factors. Although there likely is a need for serial testing, there are no data to establish with what frequency 2-dimensional echocardiography, ECG, AECG, and exercise testing should be repeated.

Conclusions

Observational data regarding risk stratification for SCD in HCM at present support testing with ECG, AECG, treadmill (or bicycle) exercise, and 2-dimensional echocardiography, in addition to obtaining a personal and family history. There are no randomized trials that use these parameters.

Patient-Based Approach to Risk Stratification

When an individual patient is being evaluated to assess his or her risk for SCD, there are several important issues that should be addressed. First and foremost, the specific goal for risk stratification for the individual patient should be identified. The choice of tests may vary if the goal is to determine the appropriateness of implanting an ICD versus titrating the aggressiveness of medical therapy versus providing the patient with information regarding his or her prognosis. At this time, there is no consensus regarding the level of risk that justifies an intervention, based on either the level of benefit or cost associated with the intervention. This is further compounded by the fact that the risk-benefit ratio of an intervention in an individual patient could differ from that observed in large-scale trials. In addition, individual and societal tolerance for risk may differ. These issues are not subject to evaluation in clinical trials, and therefore, only sound clinical judgment can be used by the practitioner to address them.

Another important issue is assessing the timing of evaluation. Early attempts at risk stratification focused on evaluating patients in the early postinfarction period (8). Many studies have demonstrated time-dependent changes in many of the risk stratification techniques discussed in this statement, including LVEF, ventricular ectopy, the SAECG, and HRV. Although there is a continued and perhaps even an enhanced risk for SCD in patients remote from their MI (202), there does remain a heightened mortality risk in the first several months postinfarction for which the cause is unclear. Most ICD primary prevention trials have specifically excluded these patients and only enrolled patients remote from their MI. In contrast, the DINAMIT study (15), which enrolled patients within 40 days of an MI who had low LVEF ($\leq 35\%$) and low HRV, did not show a survival benefit for those treated with an ICD. Similarly, the CABG-Patch trial (17) enrolled patients with coronary artery disease who had low LVEF and positive SAECGs and also found no survival benefit for those treated with an ICD. Although it is tempting to identify the SAECG or the HRV as the risk stratification technique that failed to identify the appropriate high-risk patients who would benefit from an ICD, it must be empha-

sized that these patients all had low LVEF. Because MADIT-II and SCD-HeFT, which included patients with similarly low LVEF, demonstrated a survival benefit with an ICD, it appears likely that the clinical settings (early postinfarction period or post-CABG surgery) may also affect the etiology of SCD and therefore the utility of the risk stratification techniques. Furthermore, it was recently shown that eplerenone reduced the risk of SCD by 37% at 30 days in a randomized trial of patients with acute MI, left ventricular systolic dysfunction, and heart failure (203), which suggests that alternative therapies may be required during this time period to reduce the risk of SCD. The Cardiac Arrhythmias and Risk Stratification after Myocardial infarction (CARISMA) study (204) is a multicenter study enrolling patients with an LVEF $\leq 40\%$ after acute MI in whom a loop recorder is implanted to evaluate the incidence of tachyarrhythmia and bradyarrhythmia episodes. This study will specifically evaluate the value of 24-hour AECG, SAECG, QT dispersion, T-wave alternans, and electrophysiological testing as predictors of life-threatening arrhythmias in the early postinfarction period. Risk stratification approaches and interventions will need to be related to the timing of evaluation in the patient's disease process. Further efforts to define the appropriate evaluations and treatments relative to this timing are necessary.

There are no data that identify the optimum risk stratification strategy or combination of tests to be performed. The optimal strategy should identify the vast majority of those who will experience sudden arrhythmic death and a minimal number of those who will not. No existing strategies attain this goal. There are a large number of clinical studies that have combined available techniques, with demonstrable improvement in sensitivity and specificity. Randomized ICD-intervention clinical trials have generally combined depressed LVEF with at most 1 other risk stratifier. The inadequacy of these approaches is underscored by the fact that most victims of SCD do not have low LVEF. Thus, much research is required to determine which of the myriad available tests should be performed, whether they should be performed sequentially or simultaneously, and whether a patient's risk should be assessed at some frequency in the absence of a change in clinical status. It is clear that continued progress in noninvasive risk stratification will benefit by the determination of whether the suboptimal success achieved with each approach can be improved with use of tests in combination and/or refinements in methodology to more completely detect the pathophysiological determinants of VT/VF.

Tremendous efforts have been made in developing and studying risk stratification techniques; however, at present, there are no data integrating the use of these techniques into a coherent strategy for intervention. Currently, the primary technique for stratifying risk to determine who is an appropriate candidate for an ICD for primary prevention of SCD is the LVEF. It is reasonable to place patients with LVEF $\leq 30\%$ to 35% in the highest-risk group that can be identified presently. This applies to patients with coronary artery disease and dilated cardiomyopathy. Future studies will assess whether further risk stratification within this population can be achieved.

This will require the development of a risk stratification test or strategy with high negative predictive value. In patients with coronary artery disease and LVEF $>35\%$, further testing with other risk stratification techniques (14) may be used, but data on how to apply the results of these tests are lacking. If clinical evaluation is consistent with an increased risk, further electrophysiological testing may be indicated.

The field of risk stratification requires substantial further development. Although the lack of a dominant strategy using these techniques is certainly due in part to the absence of clinical trial data, it is also important to consider that there may be limitations to the current techniques. Most of these techniques focus on the evaluation of electrical, autonomic, or anatomic substrates of the patient at rest, when the risk of SCD is low. Some of the techniques involve evaluations during exercise and the postexercise recovery period, times of relatively increased risk for SCD and ventricular arrhythmias. Clearly, there are other factors that may be implicated in the pathophysiology of SCD. Recent consensus documents have outlined the concepts of vulnerable plaque, vulnerable blood (prone to thrombosis), and vulnerable myocardium (205,206). Newer approaches that encompass a more general evaluation of "vulnerability" to sudden death, including genetic profiling, serum markers, and new imaging approaches, are necessary. Finally, if risk stratification is to be applied to a population with an overall low risk of SCD to identify a subgroup with more significant risk, it is likely that multiple tests will need to be incorporated into a risk stratification strategy; a single test, even with good sensitivity and specificity, when applied to a population with a low incidence of SCD will have a poor positive predictive value. Although it is possible that multiple positive test results could be used to identify particularly high-risk individuals, it is also possible that such a strategy would limit the proportion of the "at risk" population that can be identified.

Summary

Given the availability of therapies to prevent SCD due to otherwise fatal ventricular tachyarrhythmias, it is important to differentiate noninvasive risk stratification techniques that enhance the ability to identify SCD from total mortality. The relative ability for each of the described techniques varies, and the optimal way to combine and use these techniques in clinical practice remains unclear. Low LVEF, which is the most widely used test on which ICD intervention is recommended, does not have a particularly high discriminatory ability to identify SCD rather than non-SCD mortality. Although data exist supporting the concept that noninvasive risk stratification techniques may be useful to identify patients with low LVEF who are at low risk for SCD, this requires further testing. There are also data to support the concept that noninvasive risk stratification techniques may be useful to identify patients who do not have low LVEF who nevertheless are at substantial risk for SCD. Because most SCD occurs in this latter group, substantial effort is justified in evaluating, testing, and ultimately implementing risk stratification strategies in this group.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Jeffrey J. Goldberger	Northwestern University	RELY, Boehringer Ingelheim†; MADIT-CRT, Boston Scientific†; FIX-HF-5, Dynamics†; WBC Trial, St. Jude†	Device donations for NIH-sponsored clinical trial (PACE-MI) from Boston Scientific†; Medtronic†; St. Jude Medical†	None	Majority shareholder, Gold T-Tech (start-up medical device company involved in prevention of thromboembolism)*	Director, Path to Improved Risk Stratification (not-for-profit think tank on risk stratification for sudden cardiac death)†	Fellowship support from Boston Scientific†; Medtronic†; St. Jude Medical†
Michael E. Cain	University at Buffalo School of Medicine and Biomedical Sciences	None	None	None	None	Chair, Publications Committee, Heart Rhythm Society*	None
Stefan H. Hohnloser	Goethe University	None	None	None	None	None	None
Alan H. Kadish	Northwestern University	Medtronic†; Pfizer†; St. Jude†	None	None	None	Life Watch†	None
Bradley P. Knight	University of Chicago Hospitals	Guidant†; St. Jude†; Medtronic†	None	Guidant†; Medtronic*; St. Jude*	None	Guidant*	None
Michael S. Lauer	Cleveland Clinic Foundation	None	None	None	None	None	None
Barry J. Maron	Minneapolis Heart Institute Foundation	Medtronic*	None	None	None	None	None
Richard L. Page	University of Washington	None	None	None	None	Heart Rhythm Society*	None
Rod S. Passman	Northwestern Memorial Hospital	Medtronic*	None	None	None	None	None
David Siscovick	University of Washington, Seattle	None	None	None	None	None	None
William G. Stevenson	Brigham & Women's Hospital	None	None	St. Jude Medical*; Biosense Webster, Inc*; Medtronic Inc*; Boston Scientific, Inc*; Bard, Inc*	None	Biosense Webster, Inc*; St. Jude Medical*	None
Douglas P. Zipes	Indiana University School of Medicine	Medtronic†	None	Medtronic†	None	Medtronic†	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Sana Al-Khatib	Duke University	Medtronic†	Medtronic†	Medtronic†	None	None	None
Jeffrey Anderson	LDS Hospital	BMS (platelet inhibitors)*; Sanofi (arrhythmics)*; AstraZeneca (platelet Inhibitors)*	None	Merck (lipid lowering; speaker)†; BMS (platelet inhibitors)*; ACEI (speaker)*	None	Alteon (former consultant)*; DiaDexus (LpPLA2 test consultant)*; ThomboVision (platelet test consultant)*; Proctor-Gamble (antiarrhythmia drug consultant)*	None
Eric Bates	University of Michigan	None	None	None	None	None	None
Alfred E. Buxton	Brown Medical School	None	None	None	None	None	None
John P. DiMarco	University of Virginia Health System	Guidant†; St Jude*; Medtronic*; Sanofi-Aventis*	None	Guidant†; St Jude*; Medtronic*	None	Guidant†; St Jude*; Medtronic*; CUT*; Novartis†; Schering-Plough*	None
Leonard S. Dreifus	Retired	None	None	Merck Pharmaceutical*	None	None	None
Gregg C. Fonarow	University of California at Los Angeles Division of Cardiology	Medtronic†; Guidant*	None	Medtronic†; Guidant*	None	Medtronic†; Guidant*; Biosite*	None
Alan Forker	Mid-America Heart	Pfizer†; Merck†; Takeda†; Novartis†	None	Merck*; Takeda*	None	None	None
Michael Gold	Medical University of South Carolina Medical Center	Guidant†; Medtronic†; St Jude†	None	Guidant†; Medtronic†; St Jude†	None	Guidant†; Medtronic†	None
Gabriel Gregoratos	University of California, San Francisco	None	None	None	None	None	None
Sharon Hunt	Stanford University	None	None	None	None	None	None
Fred M. Kusumoto	Mayo Clinic Jacksonville	None	None	Medtronic*; Boston Scientific*; EP Med Systems*	None	None	None
Rita Redberg	University of California at San Francisco	None	None	Medtronic*; St Jude*	None	None	None
David S. Rosenbaum	Case Western Reserve University	CardioDx†	None	None	None	Cambridge Heart Inc.†	None
Richard Schofield	University of Florida	None	None	AstraZeneca*; AtCor Medical*; Novartis*; Pfizer*; Scios*	None	Pfizer*	None
Samuel J. Shubrooks, Jr	Beth Israel Deaconess Medical Center	None	None	None	None	None	None
David Wilber	Loyola University Medical Center	Medtronic*; Guidant*; St Jude*	None	Medtronic*; Guidant*; St Jude*	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest

†Significant.

References

- Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death: implications for the interpretation of clinical trials. *Circulation* 1996;93:519-24.
- Goldberger JJ, Weinberg KM, Kadish AH. Impact of nontraditional antiarrhythmic drugs on sudden cardiac death. In: Zipes D, Jalife J, editors. *Cardiac Electrophysiology: From Cell to Bedside*. 4th ed. Philadelphia, PA: WB Saunders, 2004:950-8.
- Myerburg RJ, Mitrani R, Interian A Jr., Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. *Circulation* 1998;97:1514-21.
- Heller RF, Chinn S, Pedoe HD, Rose G. How well can we predict coronary heart disease? Findings in the United Kingdom Heart Disease Prevention Project. *Br Med J (Clin Res Ed)* 1984;288:1409-11.
- Rose GA. *The Strategy of Preventive Medicine*. Oxford, UK: Oxford University Press, 1992.
- Wackers FJ, Berger HJ, Johnstone DE, et al. Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. *Am J Cardiol* 1979;43:1159-66.
- McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J* 2003;146:388-97.
- Bigger JT Jr., Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250-8.
- Sanz G, Castañer A, Betriu A, et al. Determinants of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. *N Engl J Med* 1982;306:1065-70.
- The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331-6.
- Volpi A, De Vita C, Franzosi MG, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis: results of the GISSI-2 data base: the Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation* 1993;88:416-29.
- Huikuri HV, Tapanainen JM, Lindgren K, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. *J Am Coll Cardiol* 2003;42:652-8.
- McClements BM, Adgey AA. Value of signal-averaged electrocardiography, radionuclide ventriculography, Holter monitoring and clinical variables for prediction of arrhythmic events in survivors of acute infarction in the thrombolytic era. *J Am Coll Cardiol* 1993;21:1419-27.
- Bailey JJ, Berson AS, Handelsman H, Hodges M. Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. *J Am Coll Cardiol* 2001;38:1902-11.
- Hohnloser SH, Kuck KH, Dorian P, et al., DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-8.
- Solomon SD, Zelenkofske S, McMurray JJ, et al., Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352:2581-8.
- Bigger JT Jr., Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997;337:1569-75.
- Moss AJ, Hall WJ, Cannom DS, et al. Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933-40.
- Moss AJ, Faddl Y, Zareba W, Cannom DS, Hall WJ, Defibrillator Implantation Trial Research Group. Survival benefit with an implanted defibrillator in relation to mortality risk in chronic coronary heart disease. *Am J Cardiol* 2001;88:516-20.
- Buxton AE, Lee KL, Hafley GE, et al., MUSTT Investigators. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: an analysis of patients enrolled in the Multicenter Unsustained Tachycardia Trial. *Circulation* 2002;106:2466-72.
- Moss AJ, Zareba W, Hall WJ, et al., Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.
- Bardy GH, Lee KL, Mark DB, et al., Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.
- Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med* 1994;331:1564-75.
- Grimm W, Christ M, Bach J, Muller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg cardiomyopathy study. *Circulation* 2003;108:2883-91.
- Kadish A, Dyer A, Daubert JP, et al., Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151-8.
- Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. *Heart* 2002;88:47-51.
- Desai AD, Yaw TS, Yamazaki T, Kaykha A, Chun S, Froelicher VF. Prognostic significance of quantitative QRS duration. *Am J Med* 2006;119:600-6.
- Nichol G, Kaul P, Huszti E, Bridges JF. Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure. *Ann Intern Med* 2004;141:343-51.
- Shamim W, Francis DP, Yousufuddin M, et al. Intraventricular conduction delay: a prognostic marker in chronic heart failure. *Int J Cardiol* 1999;70:171-8.
- Park RC, Little WC, O'Rourke RA. Effect of alteration of left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. *Circ Res* 1985;57:706-17.
- Vassallo JA, Cassidy DM, Miller JM, Buxton AE, Marchlinski FE, Josephson ME. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. *J Am Coll Cardiol* 1986;7:1228-33.
- Akar FG, Spragg DD, Tunin RS, Kass DA, Tomaselli GF. Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. *Circ Res* 2004;95:717-25.
- Freedman RA, Alderman EL, Sheffield LT, Saporito M, Fisher LD. Bundle branch block in patients with chronic coronary artery disease: angiographic correlates and prognostic significance. *J Am Coll Cardiol* 1987;10:73-80.
- McCullough PA, Philbin EF, Spertus JA, Kaatz S, Sandberg KR, Weaver WD. Resource Utilization Among Congestive Heart Failure (REACH) Study. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. *J Am Coll Cardiol* 2002;39:60-9.
- Baldasseroni S, Opasich C, Gorini M, et al., Italian Network on Congestive Heart Failure Investigators. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J* 2002;143:398-405.
- Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN. Department of Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. QRS duration and mortality in patients with congestive heart failure. *Am Heart J* 2002;143:1085-91.
- Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML, MADIT-II Investigators. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). *J Am Coll Cardiol* 2004;43:1459-65.
- Centers for Medicare and Medicaid Services. National coverage determination on implantable defibrillators. Available at: <http://www.cms.hhs.gov/coverage/download/id39-5.pdf>.
- Zimetbaum PJ, Buxton AE, Batsford W, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the Multicenter Unsustained Tachycardia Trial. *Circulation* 2004;110:766-9.
- Buxton AE, Sweeney MO, Wathen MS, et al., PainFREE Rx II Investigators. QRS duration does not predict occurrence of ventricular tachyarrhythmias in patients with implanted cardioverter-defibrillators. *J Am Coll Cardiol* 2005;46:310-6.
- Singh JP, Hall WJ, McNitt S, et al., MADIT-II Investigators. Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic

- Defibrillator Implantation Trial II (MADIT-II). *J Am Coll Cardiol* 2005; 46:1712-20.
42. Hofmann T, Meinertz T, Kasper W, et al. Mode of death in idiopathic dilated cardiomyopathy: a multivariate analysis of prognostic determinants. *Am Heart J* 1988;116:1455-63.
 43. Romeo F, Pelliccia F, Cianfrocca C, Cristofani R, Reale A. Predictors of sudden death in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1989; 63:138-40.
 44. Vaidean GD, Schroeder EB, Whitsel EA, et al. Short-term repeatability of electrocardiographic spatial T-wave axis and QT interval. *J Electrocardiol* 2005;38:139-47.
 45. Padmanabhan S, Silvet H, Amin J, Pai RG. Prognostic value of QT interval and QT dispersion in patients with left ventricular systolic dysfunction: results from a cohort of 2265 patients with an ejection fraction of $<$ or $=40\%$. *Am Heart J* 2003;145:132-8.
 46. Gang Y, Ono T, Hnatkova K, et al., ELITE II Investigators. QT dispersion has no prognostic value in patients with symptomatic heart failure: an ELITE II substudy. *Pacing Clin Electrophysiol* 2003;26: 394-400.
 47. Brendorp B, Elming H, Jun L, et al., Diamond Study Group. QTc interval as a guide to select those patients with congestive heart failure and reduced left ventricular systolic function who will benefit from antiarrhythmic treatment with dofetilide. *Circulation* 2001;103:1422-7.
 48. Elming H, Holm E, Jun L, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. *Eur Heart J* 1998;19: 1391-400.
 49. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR, ARIC Study. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J Am Coll Cardiol* 2004;43:565-71.
 50. Davey P. QT interval and mortality from coronary artery disease. *Prog Cardiovasc Dis* 2000;42:359-84.
 51. Pinsky DJ, Sciacca RR, Steinberg JS. QT dispersion as a marker of risk in patients awaiting heart transplantation. *J Am Coll Cardiol* 1997;29: 1576-84.
 52. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000;36:1749-66.
 53. Sakabe K, Ikeda T, Sakata T, et al. Comparison of T-wave alternans and QT interval dispersion to predict ventricular tachyarrhythmia in patients with dilated cardiomyopathy and without antiarrhythmic drugs: a prospective study. *Jpn Heart J* 2001;42:451-7.
 54. Brendorp B, Elming H, Jun L, Køber L, Torp-Pedersen C, DIAMOND Study Group. Danish Investigations Of Arrhythmia and Mortality On Dofetilide. Effect of dofetilide on QT dispersion and the prognostic implications of changes in QT dispersion for patients with congestive heart failure. *Eur J Heart Fail* 2002;4:201-6.
 55. Brendorp B, Elming H, Jun L, et al. QT dispersion has no prognostic information for patients with advanced congestive heart failure and reduced left ventricular systolic function. *Circulation* 2001;103:831-5.
 56. Chevalier P, Burri H, Adeleine P, et al., Groupe d'Etude du Pronostic de l'Infarctus du Myocarde. QT dynamics and sudden death after myocardial infarction: results of a long-term follow-up study. *J Cardiovasc Electrophysiol* 2003;14:227-33.
 57. Hintze U, Vach W, Burchardt H, Videbaek J, Møller M, DIAMOND Study Group. QT interval dynamics predict mortality in high-risk patients after myocardial infarction. *Scand Cardiovasc J* 2002;36: 276-81.
 58. Bonnemeier H, Hartmann F, Wiegand UK, Bode F, Katus HA, Richardt G. Course and prognostic implications of QT interval and QT interval variability after primary coronary angioplasty in acute myocardial infarction. *J Am Coll Cardiol* 2001;37:44-50.
 59. Haigney MC, Zareba W, Gentlesk PJ, et al., Multicenter Automatic Defibrillator Implantation Trial II investigators. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2004;44:1481-7.
 60. Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization in lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation* 1997;96:1557-65.
 61. Batchvarov VN, Ghuran A, Smetana P, et al. QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. *Am J Physiol Heart Circ Physiol* 2002;282: H2356-63.
 62. Gardner PI, Ursell PC, Fenoglio JJ Jr., Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. *Circulation* 1985;72:596-611.
 63. Simson MB, Untereker WJ, Spielman SR, et al. Relation between late potentials on the body surface and directly recorded fragmented electrograms in patients with ventricular tachycardia. *Am J Cardiol* 1983; 51:105-12.
 64. el-Sherif N, Gough WB, Restivo M, Craelius W, Henkin R, Caref EB. Electrophysiological basis of ventricular late potentials. *Pacing Clin Electrophysiol* 1990;13:2140-7.
 65. Wiener I, Mindich B, Pitchon R. Fragmented endocardial electrical activity in patients with ventricular tachycardia: a new guide to surgical therapy. *Am Heart J* 1984;107:86-90.
 66. Cassidy DM, Vassallo JA, Buxton AE, Doherty JU, Marchlinski FE, Josephson ME. The value of catheter mapping during sinus rhythm to localize site of origin of ventricular tachycardia. *Circulation* 1984;69: 1103-10.
 67. Manolis AS, Chiladakis JA, Malakos JS, Vassilikos V, Maounis T, Cokkinos DV. Abnormal signal-averaged electrocardiograms in patients with incomplete right bundle-branch block. *Circulation* 1997;20:17-22.
 68. Okin PM, Stein KM, Lippman N, Lerman BB, Kligfield P. Performance of the signal-averaged electrocardiogram: relation to baseline QRS duration. *Am Heart J* 1995;129:932-40.
 69. Gatzoulis KA, Carlson MD, Biblo LA, et al. Time domain analysis of the signal averaged electrocardiogram in patients with a conduction defect or a bundle branch block. *Eur Heart J* 1995;16:1912-9.
 70. Savard P, Rouleau JL, Ferguson J, et al. Risk stratification after myocardial infarction using signal-averaged electrocardiographic criteria adjusted for sex, age, and myocardial infarction location. *Circulation* 1997;96:202-13.
 71. Kirchhof P, Eckardt L, Arslan O, et al. Prolonged QRS duration increases QT dispersion but does not relate to arrhythmias in survivors of acute myocardial infarction. *Pacing Clin Electrophysiol* 2001;24: 789-95.
 72. Reinhardt L, Mäkijärvi M, Fetsch T, et al. Noninvasive risk modeling after myocardial infarction. *Am J Cardiol* 1996;78:627-32.
 73. Marques-Vidal P, Ruidavets JB, Prouteau N, Casteignau G, Delay M, Ferrières J. Prevalence of late potentials in a sample of 487 healthy, middle-aged men from southwestern France. *Pacing Clin Electrophysiol* 2000;23:888-90.
 74. el-Sherif N, Denes P, Katz R, et al., The Cardiac Arrhythmia Suppression Trial/Signal-Averaged Electrocardiogram (CAST/SAECG) Substudy Investigators. Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period. *J Am Coll Cardiol* 1995;25:908-14.
 75. Engel TR, Pierce DL, Murphy SP. Variation in late potentials and the reproducibility of their measurement. *Prog Cardiovasc Dis* 1993;35: 247-62.
 76. Goldberger JJ, Challapalli S, Waligora M, et al. Uncertainty principle of signal-averaged electrocardiography. *Circulation* 2000;101:2909-15.
 77. Pogwizd SM, Hoyt RH, Saffitz JE, Corr PB, Cox JL, Cain ME. Reentrant and focal mechanisms underlying ventricular tachycardia in the human heart. *Circulation* 1992;86:1872-87.
 78. Hood MA, Pogwizd SM, Peirick J, Cain ME. Contribution of myocardium responsible for ventricular tachycardia to abnormalities detected by analysis of signal-averaged ECGs. *Circulation* 1992;86:1888-901.
 79. Reinhardt L, Mäkijärvi M, Fetsch T, et al. Predictive value of wavelet correlation functions of signal-averaged electrocardiogram in patients after anterior versus inferior myocardial infarction. *J Am Coll Cardiol* 1996;27:53-9.
 80. Vázquez R, Caref EB, Torres F, Reina M, Guerrero JA, El-Sherif N. Reproducibility of time-domain and three different frequency-domain techniques for the analysis of the signal-averaged electrocardiogram. *J Electrocardiol* 2000;33:99-105.
 81. Gottfridsson C, Karlsson T, Edvardsson N. The short-term and long-term reproducibility of spectral turbulence and late potential variables of the signal-averaged ECG in a population sample of healthy subjects and the impact of gender, age, and noise. *J Electrocardiol* 2000;33:107-17.
 82. Bloomfield DM, Snyder JE, Steinberg JS. A critical appraisal of quantitative spectro-temporal analysis of the signal-averaged ECG: predicting arrhythmic events after myocardial infarction. *Pacing Clin Electrophysiol* 1996;19:768-77.
 83. Kavesh NG, Cain ME, Ambos HD, Arthur RM. Enhanced detection of distinguishing features in signal-averaged electrocardiograms from

- patients with ventricular tachycardia by combined spatial and spectral analyses of entire cardiac cycle. *Circulation* 1994;90:254-63.
84. Vázquez R, Caref EB, Torres F, Reina M, Ortega F, el-Sherif N. Short-term reproducibility of time domain, spectral temporal mapping, and spectral turbulence analysis of the signal-averaged electrocardiogram in normal subjects and patients with acute myocardial infarction. *Am Heart J* 1995;130:1011-9.
 85. Englund A, Andersson M, Bergfeldt L. Spectral turbulence analysis of the signal-averaged electrocardiogram for predicting inducible sustained monomorphic ventricular tachycardia in patients with and without bundle branch block. *Eur Heart J* 1995;16:1936-42.
 86. Steinbigler P, Haberl R, Brüggemann T, Andresen D, Steinbeck G. Postinfarction risk assessment for sudden cardiac death using late potential analysis of the digital Holter electrocardiogram. *J Cardiovasc Electrophysiol* 2002;13:1227-32.
 87. Ikeda T, Sakata T, Takami M, et al. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. *J Am Coll Cardiol* 2000;35:722-30.
 88. Touboul P, Andre-Fouët X, Leizorovicz A, et al., The Groupe d'Etude du Pronostic de l'Infarctus du Myocarde (GREPI). Risk stratification after myocardial infarction. A reappraisal in the era of thrombolysis. *Eur Heart J* 1997;18:99-107.
 89. Kawalsky DL, Garratt KN, Hammill SC, Bailey KR, Gersh BJ. Effect of infarct-related artery patency and late potentials on late mortality after acute myocardial infarction. *Mayo Clin Proc* 1997;72:414-21.
 90. Hartikainen JE, Malik M, Staunton A, Poloniecki J, Camm AJ. Distinction between arrhythmic and nonarrhythmic death after acute myocardial infarction based on heart rate variability, signal-averaged electrocardiogram, ventricular arrhythmias and left ventricular ejection fraction. *J Am Coll Cardiol* 1996;28:296-304.
 91. Steinberg JS, Hochman JS, Morgan CD, et al. Effects of thrombolytic therapy administered 6 to 24 hours after myocardial infarction on the signal-averaged ECG. Results of a multicenter randomized trial. LATE Ancillary Study Investigators. *Late Assessment of Thrombolytic Efficacy. Circulation* 1994;90:746-52.
 92. Evrengul H, Dursunoglu D, Kayikcioglu M, et al. Effects of a beta-blocker on ventricular late potentials in patients with acute anterior myocardial infarction receiving successful thrombolytic therapy. *Jpn Heart J* 2004;45:11-21.
 93. Karam C, Golmard J, Steg PG. Decreased prevalence of late potentials with mechanical versus thrombolysis-induced reperfusion in acute myocardial infarction. *J Am Coll Cardiol* 1996;27:1343-8.
 94. Denes P, el-Sherif N, Katz R, et al., Cardiac Arrhythmia Suppression Trial (CAST) SAECG Substudy Investigators. Prognostic significance of signal-averaged electrocardiogram after thrombolytic therapy and/or angioplasty during acute myocardial infarction (CAST substudy). *Am J Cardiol* 1994;74:216-20.
 95. Hofmann T, Burmeister A, Meinertz T. Prognostic significance of the signal averaged electrocardiogram in patients with chronic stable coronary artery disease: analysis in the time domain and by spectral temporal mapping. *Z Kardiol* 2004;93:32-42.
 96. Gomes JA, Cain ME, Buxton AE, Josephson ME, Lee KL, Hafley GE. Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction. *Circulation* 2001;104:436-41.
 97. Gold MR, Bloomfield DM, Anderson KP, et al. A comparison of T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. *J Am Coll Cardiol* 2000;36:2247-53.
 98. Bigger JT Jr., Whang W, Rottman JN, et al. Mechanisms of death in the CABG Patch trial: a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. *Circulation* 1999;99:1416-21.
 99. Scharf C, Redecker H, Duru F, et al. Sudden cardiac death after coronary artery bypass grafting is not predicted by signal-averaged ECG. *Ann Thorac Surg* 2001;72:1546-51.
 100. Turitto Turitto G, Ahuja RK, Bekheit S, Caref EB, Ibrahim B, el-Sherif N. Incidence and prediction of induced ventricular tachyarrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994;73:770-3.
 101. Turitto G, Ahuja RK, Caref EB, el-Sherif N. Risk stratification for arrhythmic events in patients with nonischemic dilated cardiomyopathy and nonsustained ventricular tachycardia: role of programmed ventricular stimulation and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1994;24:1523-8.
 102. Kondo N, Ikeda T, Kawase A, et al. Clinical usefulness of the combination of T-wave alternans and late potentials for identifying high-risk patients with moderately or severely impaired left ventricular function. *Jpn Circ J* 2001;65:649-53.
 103. Fauchier L, Babuty D, Cosnay P, Poret P, Rouesnel P, Fauchier JP. Long-term prognostic value of time domain analysis of signal-averaged electrocardiography in idiopathic dilated cardiomyopathy. *Am J Cardiol* 2000;85:618-23.
 104. Goedel-Meinen L, Hofmann M, Ryba S, Schömig A. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with non-ischemic dilated cardiomyopathy. *Am J Cardiol* 2001;87:809-12.
 105. Hohnloser SH, Klingenhöben T, Bloomfield D, Dabbous O, Cohen RJ. Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: results from a prospective observational study. *J Am Coll Cardiol* 2003;41:2220-4.
 106. Grimm W, Glaveris C, Hoffmann J, et al. Arrhythmia risk stratification in idiopathic dilated cardiomyopathy based on echocardiography and 12-lead, signal-averaged, and 24-hour Holter electrocardiography. *Am Heart J* 2000;140:43-51.
 107. Brembilla-Perrot B, Terrier de la Chaise A, Jacquemin L, Beurrier D, Houplon P. The signal-averaged electrocardiogram is of limited value in patients with bundle branch block and dilated cardiomyopathy in predicting inducible ventricular tachycardia or death. *Am J Cardiol* 1997;79:154-9.
 108. Galinier M, Albenque JP, Afchar N, et al. Prognostic value of late potentials in patients with congestive heart failure. *Eur Heart J* 1996;17:264-71.
 109. Silverman ME, Pressel MD, Brackett JC, Lauria SS, Gold MR, Gottlieb SS. Prognostic value of the signal-averaged electrocardiogram and a prolonged QRS in ischemic and nonischemic cardiomyopathy. *Am J Cardiol* 1995;75:460-4.
 110. Yi G, Keeling PJ, Goldman JH, Hnatkova K, Malik M, McKenna WJ. Comparison of time domain and spectral turbulence analysis of the signal-averaged electrocardiogram for the prediction of prognosis in idiopathic dilated cardiomyopathy. *Clin Cardiol* 1996;19:800-8.
 111. Yi G, Keeling PJ, Goldman JH, Jian H, Poloniecki J, McKenna WJ. Prognostic significance of spectral turbulence analysis of the signal-averaged electrocardiogram in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol* 1995;75:494-7.
 112. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*. 1996;93:1043-65.
 113. Fox K, Borer JS, Camm AJ, et al., Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;50:823-30.
 114. Lahiri M, Kannankeril P, Goldberger J. Assessment of autonomic function in cardiovascular disease: physiologic basis and prognostic implications. *J Am Coll Cardiol* 2008;51:1725-33.
 115. Sandercock GR, Bromley PD, Brodie DA. The reliability of short-term measurements of heart rate variability. *Int J Cardiol* 2005;103:238-47.
 116. Goldberger JJ, Challapalli S, Tung R, Parker MA, Kadish AH. Relationship of heart rate variability to parasympathetic effect. *Circulation* 2001;103:1977-83.
 117. Dekker JM, Crow RS, Folsom AR, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. *Atherosclerosis Risk In Communities. Circulation* 2000;102:1239-44.
 118. Kuch B, Parvanov T, Hense HW, Axmann J, Bolte HD. Short-period heart rate variability in the general population as compared to patients with acute myocardial infarction from the same source population. *Ann Noninvasive Electrocardiol* 2004;9:113-20.
 119. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003;107:565-70.
 120. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). *J Am Coll Cardiol* 1999;34:912-48.
 121. Kotler MN, Tabatnik B, Mower MM, Tominaga S. Prognostic significance of ventricular ectopic beats with respect to sudden death in the late postinfarction period. *Circulation* 1973;47:959-66.

122. Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischemic and nonischemic dilated cardiomyopathy: prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985;55:146-51.
123. Denes P, Gillis AM, Pawitan Y, Kammerling JM, Wilhelmson L, Salerno DM, CAST Investigators. Prevalence, characteristics and significance of ventricular premature complexes and ventricular tachycardia detected by 24-hour continuous electrocardiographic recording in the Cardiac Arrhythmia Suppression Trial. *Am J Cardiol* 1991;68:887-96.
124. Tavazzi L, Volpi A. Remarks about postinfarction prognosis in light of the experience with the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico (GISSI) trials. *Circulation* 1997;95:1341-5.
125. Hohnloser SH, Franck P, Klingenhoben T, Zabel M, Just H. Open infarct artery, late potentials, and other prognostic factors in patients after acute myocardial infarction in the thrombolytic era. A prospective trial. *Circulation* 1994;90:1747-56.
126. Cairns JA, Connolly SJ, Roberts R, Gent M, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. *Lancet* 1997;349:675-82.
127. Maggioni AP, Zuanetti G, Franzosi MG, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. *Circulation* 1993;87:312-22.
128. Julian DG, Camm AJ, Frangin G, et al., European Myocardial Infarction Amiodarone Trial Investigators. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAAT. *Lancet* 1997;349:667-74.
129. Kron J, Hart M, Schual-Berke S, Niles NR, Hosenpud JD, McNulty JH. Idiopathic dilated cardiomyopathy. Role of programmed electrical stimulation and Holter monitoring in predicting those at risk of sudden death. *Chest* 1988;93:85-90.
130. Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. *Am J Cardiol* 1983;51:507-12.
131. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R, Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;344:493-8.
132. Doval HC, Nul DR, Grancelli HO, et al., GESICA-GEMA Investigators. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. *Circulation* 1996;94:3198-203.
133. Ikegawa T, Chino M, Hasegawa H, et al. Prognostic significance of 24-hour ambulatory electrocardiographic monitoring in patients with dilative cardiomyopathy: a prospective study. *Clin Cardiol* 1987;10:78-82.
134. Pelliccia F, Gallo P, Cianfrocca C, d'Amati G, Bernucci P, Reale A. Relation of complex ventricular arrhythmias to presenting features and prognosis in dilated cardiomyopathy. *Int J Cardiol* 1990;29:47-54.
135. Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147-52.
136. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. The preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406-12.
137. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G, Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882-90.
138. Myers GA, Martin GJ, Magid NM, et al. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. *IEEE Trans Biomed Eng* 1986;33:1149-56.
139. Roach D, Wilson W, Ritchie D, Sheldon R. Dissection of long-range heart rate variability: controlled induction of prognostic measures by activity in the laboratory. *J Am Coll Cardiol* 2004;43:2271-7.
140. Tsuji H, Venditti FJ Jr., Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham heart study. *Circulation* 1994;90:878-83.
141. Kleiger RE, Miller JP, Bigger JT Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256-62.
142. Forslund L, Björkander I, Ericson M, et al. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. *Heart* 2002;87:415-22.
143. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. *Diabetes Care* 2001;24:1793-8.
144. Huikuri HV, Mäkilä TH, Airaksinen KE, et al. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation* 1998;97:2031-6.
145. Huikuri HV, Mäkilä TH, Peng CK, Goldberger AL, Hintze U, Møller M. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000;101:47-53.
146. La Rovere MT, Bigger JT Jr., Marcus FI, Mortara A, Schwartz PJ, ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998;351:478-84.
147. Camm AJ, Pratt CM, Schwartz PJ, et al., AzimiLide post Infarct surVival Evaluation (ALIVE) Investigators. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004;109:990-6.
148. Watanabe MA, Marine JE, Sheldon R, Josephson ME. Effects of ventricular premature stimulus coupling interval on blood pressure and heart rate turbulence. *Circulation* 2002;106:325-30.
149. Kawasaki T, Azuma A, Asada S, et al. Heart rate turbulence and clinical prognosis in hypertrophic cardiomyopathy and myocardial infarction. *Circ J* 2003;67:601-4.
150. Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;353:1390-6.
151. Ghuran A, Reid F, La Rovere MT, et al., ATRAMI Investigators. Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (The Autonomic Tone and Reflexes After Myocardial Infarction substudy). *Am J Cardiol* 2002;89:184-90.
152. Bonnemeier H, Wiegand UK, Friedlbinder J, et al. Reflex cardiac activity in ischemia and reperfusion: heart rate turbulence in patients undergoing direct percutaneous coronary intervention for acute myocardial infarction. *Circulation* 2003;108:958-64.
153. Davies LC, Francis DP, Ponikowski P, Piepoli MF, Coats AJ. Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. *Am J Cardiol* 2001;87:737-42.
154. Koyama J, Watanabe J, Yamada A, et al. Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure. *Circ J* 2002;66:902-7.
155. Grimm W, Schmidt G, Maisch B, Sharkova J, Muller HH, Christ M. Prognostic significance of heart rate turbulence following ventricular premature beats in patients with idiopathic dilated cardiomyopathy. *J Cardiovasc Electrophysiol* 2003;14:819-24.
156. Galvin JM, Ruskin JN. Ventricular tachycardia in patients with dilated cardiomyopathy. In: Zipes DP, Jalife J, editors. *Cardiac Electrophysiology: From Cell to Bedside*. 4th ed. Philadelphia, PA: Saunders, 2004:575-87.
157. Pitt B, Zannad F, Remme WJ, et al., Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
158. Whang W, Mittleman MA, Rich DQ, et al., TOVA Investigators. Heart failure and the risk of shocks in patients with implantable cardioverter defibrillators: results from the Triggers Of Ventricular Arrhythmias (TOVA) study. *Circulation* 2004;109:1386-91.
159. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;64:1227-34.
160. Meyer K, Westbrook S, Schwaibold M, Hajric R, Peters K, Roskamm H. Short-term reproducibility of cardiopulmonary measurements during exercise testing in patients with severe chronic heart failure. *Am Heart J* 1997;134:20-6.
161. Mahon NG, Blackstone EH, Francis GS, Starling RC 3rd, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol* 2002;40:1106-13.

162. Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med* 1998;129:286-93.
163. Imai K, Sato H, Hori M, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol* 1994;24:1529-35.
164. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351-7.
165. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol* 2001;38:1980-7.
166. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000;284:1392-8.
167. Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality. The case of stress echocardiology. *Circulation* 2001;104:1911-6.
168. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;352:1951-8.
169. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. *J Am Coll Cardiol* 2003;42:831-8.
170. Cheng YJ, Lauer MS, Earnest CP, et al. Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. *Diabetes Care* 2003;26:2052-7.
171. Gibbons RJ. Abnormal heart-rate recovery after exercise. *Lancet* 2002;359:1536-7.
172. Yawn BP, Ammar KA, Thomas R, Wollan PC. Test-retest reproducibility of heart rate recovery after treadmill exercise. *Ann Fam Med* 2003;1:236-41.
173. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. *N Engl J Med* 2003;348:781-90.
174. O'Neill JO, Young JB, Pothier CE, Lauer MS. Severe frequent ventricular ectopy after exercise as a predictor of death in patients with heart failure. *J Am Coll Cardiol* 2004;44:820-6.
175. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994;330:235-41.
176. Walker ML, Rosenbaum DS. Repolarization alternans: implications for the mechanism and prevention of sudden cardiac death. *Cardiovasc Res* 2003;57:599-614.
177. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. *Circulation* 1999;99:1385-94.
178. Bloomfield DM, Ritvo BS, Parides MK, Kim MH. The immediate reproducibility of T wave alternans during bicycle exercise. *Pacing Clin Electrophysiol* 2002;25:1185-91.
179. Turitto G, Mirandi AP, Pedalino RP, Uretsky S, El-Sherif N. Short-term reproducibility of T wave alternans measurement. *J Cardiovasc Electrophysiol* 2002;13:641-4.
180. Klingenhoben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. *Lancet* 2000;356:651-2.
181. Rashba EJ, Osman AF, MacMurdy K, et al. Enhanced detection of arrhythmia vulnerability using T wave alternans, left ventricular ejection fraction, and programmed ventricular stimulation: a prospective study in subjects with chronic ischemic heart disease. *J Cardiovasc Electrophysiol* 2004;15:170-6.
182. Tanno K, Ryu S, Watanabe N, et al. Microvolt T-wave alternans as a predictor of ventricular tachyarrhythmias: a prospective study using atrial pacing. *Circulation* 2004;109:1854-8.
183. Rashba EJ, Osman AF, MacMurdy K, et al. Exercise is superior to pacing for T wave alternans measurement in subjects with chronic coronary artery disease and left ventricular dysfunction. *J Cardiovasc Electrophysiol* 2002;13:845-50.
184. Lauer MS, Topol EJ. Clinical trials: multiple treatments, multiple end points, and multiple lessons. *JAMA* 2003;289:2575-7.
185. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation* 2004;110:1885-9.
186. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:456-63.
187. Chow T, Kereiakes DJ, Bartone C, et al. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2006;47:1820-7.
188. Gehi AK, Stein RH, Metz LD, Gomes JA. Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events: a meta-analysis. *J Am Coll Cardiol* 2005;46:75-82.
189. Eckberg DL, Sleight P. *Human Baroreflexes in Health and Disease*. Oxford, UK: Clarendon Press, 1992.
190. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992;85:177-191.
191. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 1988;78:816-24.
192. Farrell TG, Paul V, Cripps TR, et al. Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. *Circulation* 1991;83:945-52.
193. Farrell TG, Odemuyiwa O, Bashir Y, et al. Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. *Br Heart J* 1992;67:129-37.
194. Bello D, Fieno DS, Kim RJ, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol* 2005;45:1104-8.
195. Nazarian S, Bluemke DA, Lardo AC, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation* 2005;112:2821-5.
196. Maron BJ. Sudden death in young athletes. *N Engl J Med* 2003;349:1064-75.
197. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42:1687-713.
198. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:1778-85.
199. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;357:420-4.
200. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;36:2212-8.
201. Maron MS, Olivetto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295-303.
202. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004;109:1082-4.
203. Pitt B, White H, Nicolau J, et al., EPHEsus Investigators. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005;46:425-31.
204. Huikuri HV, Mähäux V, Bloch-Thomsen PE. Cardiac arrhythmias and risk stratification after myocardial infarction: results of the CARISMA pilot study. *Pacing Clin Electrophysiol* 2003;26:416-9.
205. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. *Circulation* 2003;108:1664-72.
206. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. *Circulation* 2003;108:1772-8.