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Risk Factor Assessment: Defining Populations and Individuals at Risk

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Sudden cardiac death (SCD) is defined as the unexpected natural death from cardiac causes within a short time period in a person without a cardiac condition that would appear fatal [1]. SCD is responsible for approximately 300,000 fatalities in the Unites States alone [2,3]. It is estimated that 50% of all cardiac deaths are sudden, and this proportion has remained constant despite the overall decline in cardiovascular mortality during the last decades [3]. In approximately three fourths of cases, SCD is caused by ventricular tachycardia (VT) and fibrillation (VF) [4–6], although in patients who have underlying congestive heart failure (CHF), a significant proportion of SCD is the consequence of bradycardic events or electromechanical dissociation [7].

This article summarizes the current knowledge on risk stratification in patients who have structural heart disease, notably coronary artery disease and nonischemic cardiomyopathy. Although other types of structural heart disease and inherited ion channel abnormalities are also associated with a risk of SCD, the risk stratification strategies and data in these entities are diverse and beyond the scope of this article.

Epidemiologic considerations for risk stratification

The magnitude of the problem in specific subgroups of patients prone to SCD was addressed by Myerburg in a review of the population impact of emerging implantable cardioverter/defibrillator (ICD) trials [8]. The highest incidence of SCD occurred in survivors of out-of-hospital cardiac death and high-risk post infarction subgroups, but the greatest absolute number of SCD events (population attributable risk) occurred in larger subgroups of patients at somewhat lower risk, including patients with left ventricular dysfunction, CHF, or any prior coronary events. The challenge is to identify risk factors for SCD among the large group of patients at relatively low risk, which applies, for example, directly to survivors of myocardial infarction, in an era when the prognosis has improved substantially in comparison with prior series antedating the widespread use of reperfusion therapy.

Among patients suffering from cardiac arrest, most have some form of structural heart disease, with most patients suffering from coronary artery disease [9,10], but acute myocardial infarction is seen in less than half [10,11]. In a series of 151 hearts from men who died from sudden cardiac death, the presence of acute thrombus/plaque rupture or erosion was noted in 67% of patients aged 30 to 39, but this proportion declined with age and was present in only 31% of patients ages 60 to 69 [12]. In another series of patients surviving a cardiac arrest who underwent angiography, recent coronary occlusions were noted in 48% [13].

Risk stratification aims at identifying quantitative and qualitative measurements that can serve as sensitive and specific predictors of cardiac, particularly arrhythmogenic mortality in patients with coronary disease or other cardiovascular diseases [14]. Although risk stratification is always a topic of interest from an intellectual perspective, its clinical relevance depends on the availability of a therapeutic intervention that reduces the risk of

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arrhythmogenic death. Its current relevance is greatly enhanced by the availability of medical therapies and the ICD that have been shown to reduce total and SCD mortality in selected high-risk patients [15–19].

Several potentially useful modalities can be used to stratify postinfarction patients according to their risk of an arrhythmogenic death. To exert an impact on SCD from an epidemiologically meaningful point of view, prognostic tests need to achieve a high positive predictive accuracy together with a reasonable degree of sensitivity. Otherwise, the test or the combination of tests would be too specific to have any significant impact on the epidemiologic problem of SCD simply because they yield positive findings only in a small minority of the postinfarction population. The first step toward this goal requires knowledge of the total number of sudden deaths within a specific patient population expressed as a fraction of total mortality within this group. For example, in patients who have CHF, Kjekshus [20] demonstrated that in studies in which the mean functional New York Heart Association (NYHA) class was between I and II, the overall death rate was relatively low, but 67% of deaths were sudden. In contrast, among studies with a mean functional class of IV, there was a high total mortality, but the fraction of sudden deaths was only 29%. For an intervention specific for the problem of SCD, it is important not only to identify patients at high risk of death but also to predict the most likely mode of death (ie, arrhythmic or nonarrhythmic death) because such a distinction would have a major influence on the treatment strategy. Patients with a high propensity for arrhythmic death may benefit from preventive antiarrhythmic interventions, whereas such treatment may provide no advantage or even increase the risk of mortality in patients more likely to die from nonarrhythmic death. Similarly, the likelihood of a significant benefit from an ICD would only be present in the former group. Accordingly, the various risk stratifiers currently in clinical use need to be examined not only in regard to their ability to predict total mortality but also with respect to their potential to predict specific causes of death.

A pivotal aspect of the clinical impact of risk stratification is that the methodology be applicable not only to specialized referral centers but also to the community hospital setting in which most patients with acute myocardial infarction receive care. For these reasons, invasive procedures are unlikely to gain widespread acceptance. Accordingly, current investigations focus on the development of newer methods of noninvasive risk stratification. Another prerequisite for the process of risk stratification for arrhythmic death is that it be initiated in the predischarge period. The highest risk for sudden cardiac death is within the first 12 months after the index infarction, and most events occur within the first few months [21,22]. Most recently, a substudy from the VALIANT trial reemphasized this finding clearly [23]. This trial enrolled more than 14,000 infarct survivors with left ventricular dysfunction (left ventricular ejection fraction [LVEF] $\leq$ 40%). These authors clearly demonstrated that the period of highest risk for SCD or cardiac arrest was the first month after myocardial infarction (event rate 1.4%), with a dramatic drop to a fairly constant rate of 0.14% to 0.18% per month thereafter.

Relation between the pathophysiology of sudden cardiac death and risk stratification methods

The conditions that lead to VT/VF may occur transiently or develop during the course of healing from injury to ventricular myocardium and persist. Perhaps as the most important prerequisite, death of myocardial cells results in scar formation, alterations in chamber geometry, and electrical and anatomic remodeling. Trigger or modulating factors of life-threatening arrhythmias include changes in autonomic nervous system activity, metabolic disturbances, myocardial ischemia, electrolyte abnormalities, acute volume and pressure overload of the ventricles, ion channel abnormalities, and proarrhythmic actions of cardiac and noncardiac drugs. The electrophysiologic alterations induced by these conditions initiate and maintain VT/VF most likely via re-entrant mechanisms, although abnormal automaticity, triggered activity, or combinations of these mechanisms may be operative.

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 (Fig. 1). For instance, the specific techniques aim to detect extent of myocardial damage and scar formation (LVEF, regional wall motion abnormalities), ventricular ectopy (Holter monitoring), slowed conduction (QRS duration, signal-averaged electrocardiogram [ECG]), heterogeneities

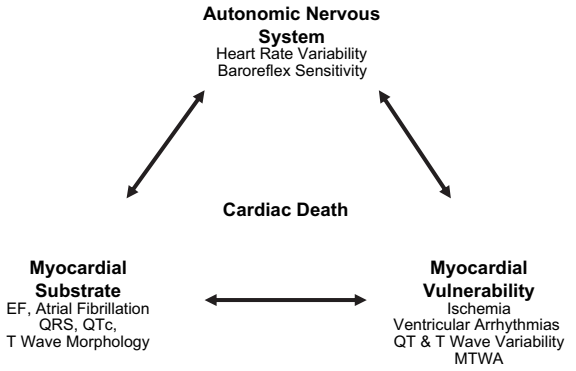

Fig. 1. Factors contributing to cardiac death and respective Holter-derived ECG parameters.

in ventricular repolarization (microvolt T-wave alternans [MTWA]), or imbalances in autonomic tone (heart rate variability [HRV], heart rate turbulence [HRT]).

Approaches to risk stratification

Clinical and demographic data

The GISSI-II Trial of 10,219 hospital survivors after thrombolytic therapy identified several clinical variables that were independently predictive of 6-month mortality. In order of importance, they were the ineligibility for an exercise test (for cardiac or noncardiac reasons), early left ventricular failure, left ventricular dysfunction in the recovery phase, age older than 70 years, electrical instability, late left ventricular failure, prior myocardial infarction, and a history of hypertension [24]. For example, in a recent study of 103,164 patients with myocardial infarction who were 65 years or older, a single-risk model (including older age, comorbidity, heart failure, reduced LVEF, and peripheral vascular disease) effectively stratified patients according to their risk of death 1 year after discharge [25].

Recently, Goldenberg and colleagues [26] attempted to develop a simple risk stratification score for primary ICD therapy based on the MADIT II population. Using best-subset proportional-hazards regression analysis, the following five risk factors for all-cause mortality were identified: age, NYHA class, blood urea nitrogen level, atrial fibrillation, and QRS duration. The risk score was constructed as a count of risk factors identified in each patient. Almost one third of the entire patient population had a risk score of 0; in this group, crude mortality was similar in the conventional and the ICD groups. By contrast, among patients with one or more risk score factors, crude mortality rates were lower in ICD patients than among patients in the control arm of the study (2-year mortality rate in the ICD group 15% versus 27% in the control arm, $P < .001$). On the other hand, among patients with three or more risk factors, mortality rates were similar in both groups. Based on these findings, the authors noted that a U-shaped pattern for ICD efficacy exists in a population of coronary patients with reduced LV function (Fig. 2). The ICD was found to have a pronounced benefit in the intermediate-risk patients but attenuated efficacy in lower and higher risk subsets. These observations may have important clinical implications when deciding on ICD therapy in individual patients.

Ventricular function

Ventricular function as defined by the predischarge LVEF has been recognized as a major determinant of late mortality for decades [14,22,27,28]. Although the proportion of patients with impaired left ventricular function has declined after reperfusion therapy, the correlation between impaired LVEF and late mortality persists [27]. In comparison with earlier studies, recent series suggest that the curve relating mortality to LVEF has "shifted to the left," implying that for a given degree of left ventricular dysfunction, the increase in mortality is somewhat less than previously reported. A recent study of 313 patients, all of whom had a patent infarct-related artery at the time of discharge, identified that an LVEF of 35% or less still had a positive predictive value of

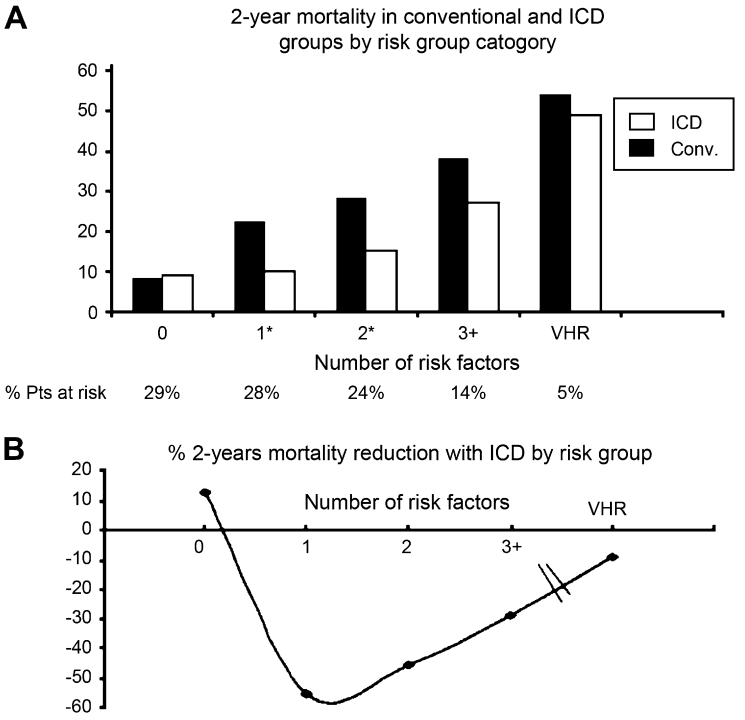

Fig. 2. U-shaped curve for ICD efficacy. (*A*) Two-year Kaplan-Meier mortality rates in the ICD and conventional therapy groups. (*B*) The corresponding 2-year mortality rate reduction with an ICD, by risk score, and in very high risk (VHR) patients. * = $P < .05$ for the comparison between the conventional therapy and the ICD groups. (*Adapted from* Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288–96; with permission.)

28% for cardiac death or sustained ventricular arrhythmias during follow up [29].

In another series of patients with an anterior myocardial infarction, all of whom underwent primary percutaneous transluminal coronary angioplasty, the presence of restrictive diastolic filling as defined by deceleration time on echocardiography of less than 130 msec was associated with a 2-year mortality rate over a mean of 32 months of 21% versus only 3% in patients without restrictive features [30]. Data such as these point to the presence of smaller patient subgroups (30% of the total in this series) who may benefit from further risk stratification. On the other hand, these data also suggest that the remaining 70% of patients with an excellent prognosis might not require any additional risk stratification, given a mortality rate of only 3% at 2 years. What is important in this study is that the predictive power of diastolic dysfunction was independent of LVEF.

The use of LVEF as the predominant risk stratifier has serious limitations, however, because LVEF lacks sensitivity for prediction of SCD. This is emphasized by the fact that less than 50% of infarct survivors who die suddenly have a LVEF of 30% or less. In a recent analysis of the MUSTT data [31], the relationship between 25 variables and total and arrhythmic mortality was examined in 674 patients not receiving antiarrhythmic therapy. In multivariate analysis, the variables with the greatest prognostic impact were NYHA class, history of heart failure, nonsustained VT, enrollment as inpatient, and atrial fibrillation. From this analysis, it could be shown that patients whose only risk factor is LVEF 30% or less have a predicted 2-year arrhythmic death risk of less than 5% [31]. Importantly, approximately 25% of patients whose LVEF was 30% or less did not have additional risk factors. The conclusion of this study was that in these patients the ICD does not demonstrate significant benefit, whereas patients with a LVEF more than 30% but with additional risk factors may derive more benefit from device therapy.

Ambulatory electrocardiographic monitoring

Holter monitoring is a comprehensive tool for identifying and quantifying factors that might contribute to the mechanism of SCD (see Fig. 1). Historically, detecting and quantifying Holter-recorded ventricular arrhythmias was the first ECG-based approach to determine the risk of patients and implement antiarrhythmic therapy [1]. There is clear association between the detection of ventricular arrhythmias (ventricular premature beats [VPBs], non-sustained ventricular tachycardia [NSVT]) on Holter ECG in patients after myocardial infarction with left ventricular dysfunction and the risk for mortality. Primary prevention of sudden death with ICD therapy was introduced by the MADIT and MUSTT trials in patients with documented nonsustained VT and inducibility of ventricular tachyarrhythmias [15,16]. After the MADIT II [18] and SCD-HeFT [32] trials, however, LVEF of 30% or less is considered a sufficient risk stratifier without the need for documenting Holter-detected ventricular arrhythmias or inducible VT. Accordingly, the incremental risk stratification value provided by the finding of spontaneous ventricular arrhythmias in patients with LVEF of 35% or less is unclear. On the other hand, patients with LVEF between 35% and 40% may warrant Holter ECG recordings to assess for nonsustained VT, because this group has been shown to benefit from an ICD if VT is induced at electrophysiologic study. Patients with preserved left ventricular function after myocardial infarction are generally at low risk, and current data suggest that they would not benefit from undergoing risk stratification using Holter ECG recording.

QRS width, signal-averaged electrocardiogram

A broad QRS complex is associated with an increased risk of mortality, and patients with conduction disturbances do not benefit much from signal-averaged ECG (SAECG) analyses. The presence of late potentials or prolonged filtered QRS duration in SAECG in patients with normal QRS duration on standard ECG indicates increased risk of cardiac events, however. Data from MUSTT trial [33] in 1925 patients demonstrated that filtered QRS duration longer than 114 msec was significantly associated with the primary study endpoint (arrhythmic death or cardiac arrest) after adjustment for clinical covariates. Patients with an abnormal SAECG had a 28% incidence of primary endpoints in comparison to 17% in patients with normal SAECG ($P < .001$) during 5-years' follow-up. Cardiac death and total mortality also were significantly higher. In this study, combination of prolonged filtered QRS duration longer than 114 msec and LVEF less than 30% identified a high-risk subset of patients. This finding was of particular importance because the clinical usefulness of inducible ventricular tachycardia was found to be limited in this study.

Data also indicate that the combination of abnormalities in SAECG with positive results of T-wave alternans test might be useful in identifying high-risk individuals in the early postinfarction period [34,35]. Bayley et al [36] suggested the use of SAECG together with LVEF as first steps of risk stratification process in postinfarction patients. Patients with normal SAECG and preserved left ventricular function have a low risk of arrhythmic events (approximately 2% over 5-year period), whereas patients with abnormal SAECG and depressed LVEF have a high risk of such events (approximately 38%). Intermediate groups, with either test abnormal, require further stratification using Holter-based HRV and ventricular arrhythmia analysis or programmed ventricular stimulation. Ultimately, this strategy is likely to identify most patients eligible for ICD therapy and patients who may not need this treatment. In summary, ample data show that an abnormal SAECG may identify patients with prior myocardial infarction at risk for SCD. Given the high negative predictive value of this test, it may be useful for identifying patients at low risk. Routine use of SAECG for identifying patients at high risk for SCD seems to be not adequately supported at this time, however.

Microvolt T-wave alternans

The presence of subtle beat-to-beat changes in the in the amplitude of the T-wave in the surface ECG, which is termed microvolt T-wave alternans (MTWA), has been shown to be associated with an increased risk of SCD or other serious ventricular tachyarrhythmic events [34,35,37]. Particularly in patients with ischemic and nonischemic cardiomyopathy, assessment of MTWA has been shown to be useful for prediction of arrhythmic complications during the subsequent course of these patients. For instance, a report on 129 patients with ischemic cardiomyopathy found that over 24 months' follow-up, no major arrhythmic event or SCD occurred in patients who tested negative; on the other hand, in MTWA-positive

patients or patients with an indeterminate test result, the event rate was 15.6% [38].

Bloomfield and coworkers [39] recently reported their findings in 177 MADIT II-like patients in whom they assessed MTWA and whom they followed for 2 years. They found that a positive MTWA was associated with a higher mortality rate than that associated with a prolonged QRS duration of more than 120 msec. The actuarial mortality rate was 17.8% in patients with a positive MTWA compared with only 3.8% in patients who tested negative for MTWA (hazard ratio 4.8, 95% confidence interval 1.1–20.7, $P = .02$). Several additional studies confirmed these early findings (Fig. 3). It is of particular note that in all studies evaluating MTWA for arrhythmic risk stratification, MTWA carried a high negative predictive value of between 96% and 100%. This finding indicates that analysis of MTWA may be particularly helpful to avoid unnecessary ICD implantations in patients with depressed LV function who test negative for MTWA.

Similarly, there are at least four prospective studies about the predictive value of MTWA after myocardial infarction. In all but one of these studies, assessment of a positive (abnormal) MTWA carried prognostic implications with respect to future arrhythmic events and SCD [34,40–42]. One of these studies deserves more detailed considerations because currently, risk stratification after acute myocardial infarction relies predominantly on the presence of reduced LV function. Little is known about the value of risk markers in infarct survivors with preserved LV function. Accordingly, Ikeda and colleagues [42] measured MTWA in 1014 patients with a LVEF of 0.40 or more at 48 ± 66 days after an acute myocardial infarction along with 10 other commonly used risk variables. Over a mean of 32 ± 14 months, a positive MTWA, nonsustained VT, and ventricular late potentials were predictors of SCD or ventricular tachyarrhythmias (primary study endpoint). On multivariate analysis, a positive MTWA test result was the most significant predictor (HR 19.7).

In conclusion, these studies indicate that MTWA assessment may yield prognostic information regarding ventricular tachyarrhythmic events in infarct survivors even in patients with preserved LV function. It seems clear, however, that MTWA evolves during the subacute phase of myocardial infarction, indicating that its determination should be postponed until some weeks after the index event.

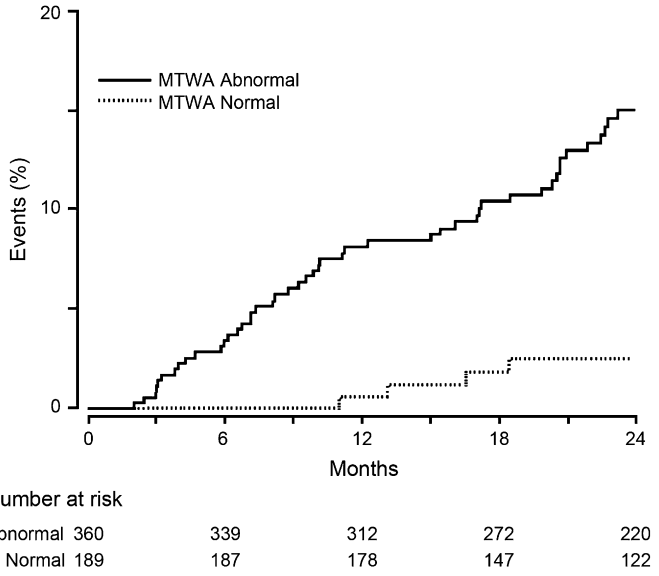

Fig. 3. Kaplan-Meier mortality curves for patients with normal versus abnormal MTWA test results. During the 2-year follow-up period, only four events occurred in 189 patients with a negative MTWA compared with 47 in the nonnegative group. Nonnegative test results comprised positive tests ($n = 162$, 2-year event rate 12.3%) and indeterminate test ($n = 198$, 2-year event rate 17.5%). (*From* Bloomfield D, Bigger J, Steinman R, 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;47:460; with permission.)

Measures of autonomic control

Numerous studies explored the prognostic value of HRV parameters for predicting outcomes in postinfarction patients [43–47]. They consistently showed that depressed HRV is associated with increased mortality. Limited data are available regarding the prognostic significance of HRV parameters for predicting sudden or arrhythmic death. The limited evidence for the association between depressed HRV parameters and SCD might be caused by the difficulty in categorizing sudden or arrhythmic nature of death but also could be because of lack of strong evidence for this association. HRV also operates differently in different patient populations depending not only on the disease but also on advancement of the disease process. HRV parameters predict well CHF worsening and total mortality in CHF patients, whereas the predictive value of HRV for SCD is limited. Similarly, there are no studies linking HRV with inducibility at electrophysiologic testing, which further indicates that HRV might not be the right approach to identify susceptibility to arrhythmias. Reported associations with arrhythmic events are most likely driven by CHF, which predisposes to SCD itself.

HRT is a new method to evaluate the response of sinus beats to single ventricular premature beats [48]. The normal response to VPBs consists of immediate acceleration with subsequent deceleration of heart rate, whereas a blunted response, which does not show such a reaction, is considered as a noninvasive sign of impaired baroreflex sensitivity. Schmidt and coworkers [48] demonstrated that HRT quantified using two parameters that describe turbulence onset and turbulence slope was an independent predictor of total or cardiovascular mortality in two large post infarction populations. This observation was further substantiated by recent analysis of data in postinfarction patients from the ATRAMI study [49] and the ISAR study [50], with most patients treated with primary coronary interventions. As with HRV parameters, there is no support for direct association between HRT parameters and sudden death. Finally, the method of HRT assessment was recently even more refined by characterizing the deceleration and acceleration of heart rate [51]. This finding led to the determination of deceleration capacity, which could be shown to be a significant predictor of mortality after myocardial infarction.

In summary, strong evidence links depressed HRV and abnormal HRT with cardiac mortality. These methods should be used in the risk stratification process, however, with full realization that their predictive value might not be directly related to sudden death or arrhythmic events.

Invasive electrophysiological testing

Testing inducibility of ventricular tachycardia in postinfarction patients became a standard modality for identifying high-risk individuals prone to sudden death. MADIT and MUSTT were designed to enroll postinfarction patients with depressed LVEF who presented with nonsustained VT and inducibility of ventricular tachyarrhythmias during invasive electrophysiologic testing [15,16]. These primary prevention trials with the use of ICDs demonstrated that the risk stratification algorithm was able to select a subset of postinfarction patients with high mortality risk. Secondary analysis from MUSTT [52] revealed that despite significant difference in outcome between inducible patients enrolled in the trial and noninducible patients enrolled in a registry, electrophysiological (EP) inducibility was found of limited use because the 5-year mortality rate in inducible patients was 48% compared with 44% in noninducible patients.

Later, data from MADIT II showed that there is no need for additional risk stratifiers (including EP testing) when LVEF is so low. In more than 80% of patients randomized to the ICD arm of MADIT II, invasive EP testing with attempt to induce tachyarrhythmias was performed at the time of ICD placement. VT inducibility, observed in 40% of studied patients, was not effective in identifying patients with cardiac events defined as ventricular tachycardia, ventricular fibrillation, or death. These observations from both MUSTT and MADIT II subanalyses suggest that in patients with substantially depressed left ventricular function, EP inducibility should not be considered a useful predictor of outcome. It is possible, however, that inducibility might have much better predictive value in postinfarction patients with LVEF more than 30% or more than 35%.

Risk stratification in nonischemic cardiomyopathy

The previous sections focused on postinfarction patients, whereas a growing number of patients who have CHF and nonischemic

Table 1
Prospective studies using microvolt T-wave alternans for risk stratification in patients with dilated cardiomyopathy

Study (reference)	Patient population	Patients (N)/follow-up (mo)	Primary study endpoint	% patients with nonnegative MTWA	Main result
Klingenheben [56]	CHF, LVEF < 0.45, ICMP 70%, NICMP 30%	107 14.6 mo	Arrhythmic death or VT/VF	70%	MTWA = predictor of PEP (HR ∞)
Hohnloser [38]	ICMP, LVEF <0.35	129 24 mo	Arrhythmic death	73%	MTWA = predictor of PEP (HR ∞)
Bloomfield [39]	ICMP, LVEF < 0.35	177 20 ± 6 mo	2 year all-cause mortality	68%	MTWA = predictor of PEP (HR 4.8)
Hohnloser [53]	NICMP	137 14 ± 6 mo	Arrhythmic death or resuscitated VF/VT	75%	MTWA = predictor of PEP (HR 3.4)
Grimm [54]	NICMP	343 52 ± 21	Arrhythmic death or resuscitated VF/VT	NA	MTWA not predictive of PEP
Bloomfield [57]	ICMP (49%), NICMP (51%)	549 20 ± 6 mo	All-cause mortality or non-fatal VT/VF	66%	MTWA = predictor of PEP (HR 6.5)
Chow [58]	ICMP, LVEF < 0.35	768 18 ± 10 mo	All-cause mortality	67%	MTWA = predictor of all-cause (HR 2.2) and arrhythmic mortality (HR 2.3)
Salerno-Uriarte [55]	NICMP, LVEF < 0.40	446 NA	Cardiac death, life-threatening ventricular arrhythmias	65%	MTWA = predictor of PEP (HR 4.0)

Abbreviations: CHF, congestive heart failure; HR, hazard ratio; ICMP, ischemic cardiomyopathy; NICMP, nonischemic cardiomyopathy; PEP, primary endpoint.

cardiomyopathy is being seen by cardiologists and is considered for prophylactic ICD therapy. DEFINITE [19] was a recent trial that evaluated the effects of ICD therapy on mortality in patients with nonischemic cardiomyopathy. Approximately half of patients enrolled in SCD-HeFT [32] had nonischemic cardiomyopathy. Both these studies indicated that ICD therapy reduces mortality in nonischemic cardiomyopathy patients. Following these findings, new indications for ICD in the United States include nonischemic cardiomyopathy with LVEF of 30% or less.

The question remains as to how to identify patients with nonischemic cardiomyopathy who might benefit from ICD therapy more than other individuals. Invasive EP testing with inducibility of ventricular arrhythmias is not useful as a risk stratification method. Several noninvasive techniques were explored, including presence of nonsustained VT, abnormal signal averaged ECG, HRV, and recently, MTWA. Among these noninvasive modalities, MTWA seems to be of increasing interest in dilated cardiomyopathy patients. For instance, Hohnloser et al [53] studied 137 dilated cardiomyopathy patients followed for a mean 14 months and found that decreased baroreflex sensitivity and presence of MTWA were the only two significant predictors of arrhythmic events outperforming other tested parameters, including NSVT, SAECG, LVEF, and HRV. At least one other study could not confirm these observations, however [54].

Several other studies have examined the prognostic yield of MTWA determination in this population (Table 1). Recently, the largest prospective study on the use of MTWA for risk stratification in nonischemic cardiomyopathy was published [55]. In an Italian multicenter study, 464 patients were tested for MTWA and subsequently followed for 18 to 24 months for the primary endpoint of cardiac death and life-threatening arrhythmias. For patients who tested MTWA positive, the unadjusted and adjusted hazard ratios were 4.0 (95% confidence interval 1.4–11.4; $P = .002$) and 3.2 (1.1–9.2; $P = .013$). Importantly, the negative predictive value of the test was more than 97%. The authors concluded that an abnormal MTWA test result in patients with nonischemic cardiomyopathy, NYHA II/III CHF, and a LVEF less than 40% selects a group of patients at high risk for SCD. Conversely, patients with unremarkable test results have a benign prognosis and are not expected to derive much benefit from ICD therapy.

Summary

Vigorous efforts have been made in developing noninvasive stratification methods. Unfortunately, a coherent strategy for intervention based on data integrating the results of these techniques is still lacking. Currently, the primary technique for stratifying risk to determine who are appropriate candidates for an ICD for primary prevention of SCD is the LVEF. It is reasonable to place patients with LVEF of 30% to 35% or less in the highest risk group that can be identified currently. 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. More randomized intervention trials based on the results of risk stratification techniques (ie, assessment of MTWA or HRT) are needed. Although the lack of a dominant strategy using these techniques is caused partly by 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 post-exercise recovery period—times of relatively increased risk for SCD and ventricular arrhythmias. Other factors may be implicated in the pathophysiology of SCD. 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 has has 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.

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