

Sudden Cardiac Death Compendium

Circulation Research Compendium on Sudden Cardiac Death

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Gordon Tomaselli, Editor

Sudden Cardiac Death Risk Stratification

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Abstract: Arrhythmic sudden cardiac death (SCD) may be caused by ventricular tachycardia/fibrillation or pulseless electric activity/asystole. Effective risk stratification to identify patients at risk of arrhythmic SCD is essential for targeting our healthcare and research resources to tackle this important public health issue. Although our understanding of SCD because of pulseless electric activity/asystole is growing, the overwhelming majority of research in risk stratification has focused on SCD-ventricular tachycardia/ventricular fibrillation. This review focuses on existing and novel risk stratification tools for SCD-ventricular tachycardia/ventricular fibrillation. For patients with left ventricular dysfunction or myocardial infarction, advances in imaging, measures of cardiac autonomic function, and measures of repolarization have shown considerable promise in refining risk. Yet the majority of SCD-ventricular tachycardia/ventricular fibrillation occurs in patients without known cardiac disease. Biomarkers and novel imaging techniques may provide further risk stratification in the general population beyond traditional risk stratification for coronary artery disease alone. Despite these advances, significant challenges in risk stratification remain that must be overcome before a meaningful impact on SCD can be realized. (*Circ Res.* 2015;116:1907-1918. DOI: 10.1161/CIRCRESAHA.116.304493.)

Key Words: death, sudden, cardiac ■ risk assessment ■ tachycardia, ventricular

Sudden cardiac death (SCD), generally defined as death within 1 hour of symptom onset or during sleep in a patient who was previously stable, is a clinical syndrome that is a final common pathway of several disease conditions and states. The syndrome includes arrhythmic and nonarrhythmic causes. Arrhythmic SCD may be preventable, treatable, or a terminal

manifestation of severe underlying heart disease. Arrhythmic SCD may also represent either a personal or societal acceptable outcome for patients with advanced heart disease, in part, responsible for the dramatic variations in per capita use of the implantable cardioverter defibrillator in different countries.¹ Because of the potentially treatable arrhythmias that form a

Original received October 29, 2014; revision received January 26, 2015; accepted March 2, 2015. In April 2015, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 13.84 days.

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Circulation Research is available at <http://circres.ahajournals.org>

DOI: 10.1161/CIRCRESAHA.116.304493

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CCTA	coronary computed tomographic angiography
HRV	heart rate variability
HRT	heart rate turbulence
ICD	implantable cardioverter defibrillator
ICM	implantable cardiac monitor
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
PET	positron emission tomography
PVC	premature ventricular complex
SCD	sudden cardiac death
SCD-VT/VF	sudden cardiac death due to ventricular tachycardia or fibrillation
SPECT	single photon emission computed tomography
TWA	T-wave alternans

major part of this syndrome, there has been an array of research activities into approaches to identify patients at risk, preventive therapies (ie, β -blockers), and reactive therapies (cardiopulmonary resuscitation and implantable cardioverter defibrillators [ICDs]). These studies have provided important insights and illustrate the multidimensional nature of the problem. In this article, we will review risk stratification approaches for arrhythmic SCD.

Arrhythmic SCD may be because of ventricular fibrillation (VF)/ventricular tachycardia (VT) [SCD-VT/VF] or asystole/pulseless electric activity. Epidemiological studies suggest that there has been a decline in cardiac arrest caused by VT/VF and a concomitant increase in pulseless electric activity/asystole.² Although the cause for this is unclear, at least part of the explanation lies in improved therapy for acute coronary syndromes and chronic coronary artery disease (CAD). Therapies that treat or prevent myocardial infarction (MI) have a major impact on the occurrence of SCD-VT/VF.^{3–5} The majority of research in risk stratification has focused on SCD-VT/VF as the pathophysiologic understanding, outcomes, and available treatments for this are far superior than for pulseless electric activity/asystole.⁶ SCD from pulseless electric activity/asystole is emerging as an important focus for future investigation, but risk stratification in this area is in its infancy.⁷ Consequently, this review focuses on risk stratification of SCD-VT/VF.

Contemporary risk stratification for SCD-VT/VF in clinical practice centers almost solely around which patients should receive ICDs. This is problematic because ICDs, in their current form, are resource-intensive and not without risk, limiting their scope to those at highest risk for SCD-VT/VF, particularly in healthcare systems with scarce resources. Implantation of ICDs in only those at high risk also ignores the fundamental epidemiology of SCD-VT/VF. The majority of SCD-VT/VF cases occurs in patients not traditionally considered a high-risk group and frequently, SCD-VT/VF is the first manifestation of cardiac disease.⁸ Major society guideline recommendations for ICD implantation are also largely based

on inclusion criteria of large randomized trials that demonstrated survival benefit for ICD therapy.^{9,10} Yet actual risk of SCD-VT/VF is more nuanced and dependent on multiple factors.^{11,12} Therefore, current guidelines may not represent optimal allocation of health resources from both a financial and a population health perspective.

More accurate risk stratification is required for any meaningful impact on the population burden of SCD-VT/VF. Despite the complexity of the problem, there have been considerable recent advances in our understanding of SCD-VT/VF that show promise in enhancing our ability to identify those at risk.

Important Concepts in Risk Stratification

Before discussing existing and novel methods for assessing risk, it is worthwhile to examine selected fundamental concepts in risk stratification of SCD.

The first is that risk in complex cardiac conditions with varying phenotype (ie, ischemic heart disease) is almost never dichotomous but rather continuous, which is particularly true in the case of SCD-VT/VF. Because indications for therapy in SCD-VT/VF are often presented as dichotomous, it can be natural to presume underlying risk is also dichotomous.⁸ However, the risk of SCD-VT/VF is the result of a complex interaction of several factors that result in a continuous spectrum of risk. Furthermore, this risk is dynamic and modulated by a variety of environmental factors, as well as biorhythms (time of day, day of week, and season).^{13,14} In SCD-VT/VF and other complex diseases, no single variable has adequate discrimination to dichotomize risk. The notion of continuous risk has been well applied to other disease states, such as CAD and cardiac surgery.^{15,16} Yet the adoption of continuous risk models to SCD-VT/VF has not gained traction to date. Practice guidelines for treatment inevitably require some categorization of patient risk. Such categorization is not only entirely based on underlying risk of SCD-VT/VF but also influenced by the risk/benefit of treatment, inclusion criteria of pertinent clinical trials, and cost-effectiveness analyses.

Perhaps an even more important concept in SCD-VT/VF is that of competing risk. All patients at risk for SCD-VT/VF will also be at risk for nonsudden death from cardiovascular and noncardiovascular causes. Many of the identified risk factors for SCD-VT/VF, such as functional status, intraventricular conduction delay, and concomitant atrial fibrillation, are also risk factors for nonsudden death.^{11,12,17} Among patients at high risk of SCD-VT/VF, certain patients may be at high concomitant risk of nonsudden death; in these patients, the benefit of ICD therapy might be small despite the increased risk of SCD-VT/VF. Optimal risk stratification in SCD-VT/VF would identify those patients at high risk of VT/VF but in whom the competing risk of nonsudden death is low, thereby identifying those who would benefit most from targeted intervention.

Not only is the risk of SCD-VT/VF dependent on multiple factors, but also the risk of an individual can change markedly over time. Risk assessment using only a single, static assessment is likely to be inadequate for accurate long-term prediction. Individual variables frequently change over time.

For example, considering only the immediate post-MI left ventricular (LV) function in risk stratification ignores the frequent improvements that occur in the first few months or the development of adverse remodeling that may occur over a period of years.¹⁸ Furthermore, the importance of certain factors in determining risk may also change over time. In both the REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) and Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) studies, measures of impaired autonomic function assessed within the first month after MI were poorly predictive of SCD.^{19,20} Yet these measurements became predictive when measured at 2 to 4 months. Thus, risk assessment for SCD-VT/VF must be a dynamic process and will require periodic reassessment.²¹

Risk Stratification in LV Dysfunction and After MI

MI and LV dysfunction are the 2 conditions that have the highest population attributable risk for SCD-VT/VF (each >30%).²² These conditions frequently overlap and patients with either or both conditions are at high risk of SCD-VT/VF, and the majority of research into risk prediction of SCD-VT/VF has focused on these populations.

The pathophysiology of the development of VT/VF in the presence of LV dysfunction or MI represents a complex interplay between multiple factors.²³ These factors can be broadly grouped into (1) anatomic substrate (generally fixed) abnormalities, (2) autonomic abnormalities, and (3) measures of

arrhythmia vulnerability (ie, ECG repolarization abnormalities). A further approach to risk stratification aims to provoke or identify subclinical arrhythmias that may be precursors for VT/VF. Finally, the development of VT/VF is also influenced by patient-level factors (such as age, comorbidities, and functional status), biorhythms (such as time of day and season), and genetic factors. The influence of genetic factors in SCD is discussed in a separate article in this compendium.^{23a}

A wide range of tools has been evaluated for risk stratification and the sheer number can be daunting for the clinician and researcher alike. It is useful to classify these tools within the larger pathophysiologic framework of SCD-VT/VF and a summary is presented in Table 1.

Methods for Identifying Fixed Substrate Abnormalities

Cardiac Imaging

The vast majority of ventricular arrhythmias in patients with MI or LV dysfunction arise from diseased myocardium and particularly from regions of myocardial scar.^{24–26} Myocardial scar may lead to both slow and heterogeneous electric conduction within the heart, both of which are central to the development of VT and VF. Because there is no current treatment for myocardial scar, it is considered a fixed substrate with a persistent risk of SCD-VT/VF. Consequently, evaluation and quantification of scar, broadly defined to include the peri-infarction border zone, may provide a useful tool for risk stratification. There are limitations to the use of scar as a risk measure of for SCD-VT/VF. Not all scar is necessarily arrhythmogenic and scar itself can be heterogeneous, as outlined below. Furthermore, although scar is considered relatively fixed, the electric properties of scar undoubtedly evolve over time.

A crude marker for overall scar burden is global LV systolic function, which is most frequently quantified as LV ejection fraction (LVEF). The link between reduction in LVEF and risk of SCD-VT/VF in patients with MI and or LV dysfunction is well established.^{27,28} LVEF has numerous advantages in that it can be measured by a variety of means that are ubiquitously available (including echocardiography, angiography, nuclear imaging, and MRI), and the measurement itself is relatively easy although susceptible to substantial differences related to technique and loading conditions, among other factors. Consequently, LVEF became the major inclusion criteria for trials evaluating ICDs for the primary prevention of SCD.^{29–31} The positive results of these trials directly led to the incorporation of LVEF as the major determinant of who should receive ICD therapy.^{9,10}

There are serious limitations to LVEF as a risk stratification tool. LVEF is a potent predictor of overall mortality and non-SCD, which limits its specificity as a predictor for SCD-VT/VF.²⁷ As such, LVEF alone has been insufficient to predict patients who would benefit from ICD therapy post MI and after bypass surgery.^{32,33} Perhaps most importantly, LVEF, as a global measure of heart function, is only loosely correlated with the amount of myocardial scar.³⁴ As a result, the predictive ability of LVEF alone for SCD-VT/VF is modest.

A variety of imaging modalities allow for more direct imaging of scar. Echocardiography allows for indirect scar

Table 1. Summary of Available Risk Stratification Tools for Sudden Cardiac Death-Ventricular Tachycardia/Fibrillation in Patients With Myocardial Infarction or Left Ventricular Dysfunction

Domain	Technique
Anatomic substrate abnormalities	
Cardiac imaging	Global left ventricular function/ejection fraction
	Myocardial scar assessment (MRI, SPECT, PET)
ECG depolarization abnormalities	ECG QRS duration
	ECG QRS fractionation
	Signal-averaged ECG
Autonomic measures	Heart rate variability
	Heart rate turbulence
	Baroreceptor sensitivity
	Imaging: SPECT (MIBG), PET
	(¹¹ C-meta-hydroxyephedrine)
ECG repolarization measures	T-wave alternans
	QT dispersion/variability
	QRS-T angle
	QT interval
Provocative testing/screening for nonsustained arrhythmias	Electrophysiology study
	Ventricular ectopy and nonsustained VT on ambulatory ECG monitoring

MIBG indicates meta-iodobenzylguanidine; PET, positron emission tomography; SPECT, single photon emission computed tomography; and VT, ventricular tachycardia.

imaging through analysis of wall motion and deformation. Advances in tissue Doppler techniques, namely strain imaging, have allowed for more specific identification of scar beyond identification of wall motion abnormalities.³⁵ In a large, multicenter, prospective study of 569 patients >40 days post MI, strain imaging provided better prediction of arrhythmic events (VT/VF) and SCD than LVEF, particularly in patients with LVEF >35%.³⁶

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) can also identify scar by visualizing areas with irreversible perfusion defects. Each of these modalities has been shown to predict arrhythmic and cardiovascular death among patients with MI.^{37,38} Because of their reliance on perfusion, SPECT and PET imaging may be less useful for nonischemic causes of LV dysfunction. Yet, in patients with MI, SPECT and PET imaging can simultaneously assess scar, ischemic burden, hibernating myocardium, and even autonomic function.³⁹

Cardiac MRI is able to identify myocardial scar by delayed enhancement imaging after gadolinium administration. It has a much greater spatial resolution than SPECT or PET imaging and is not dependent on vascular perfusion, allowing for identification of scar in nonischemic processes. Quantification of total scar burden by MRI has been shown to be superior to LVEF in predicting VT/VF and appropriate ICD therapy in both ischemic and nonischemic populations. Yet simple quantification of scar burden does not fully reflect the complex pathophysiology of scar-based VT/VF. Electrophysiology mapping has revealed that most VT circuits are found in scar with surviving islands of electric activity.⁴⁰ Thus, heterogeneous scar with both dense, electrically inactive and less dense, electrically active areas may be more arrhythmogenic. Cardiac MRI is capable of differentiating heterogeneous zones, which appear as intermediate intensity delayed enhancement, from dense scar and such findings correlate well with results of electrophysiology voltage mapping of VT circuits.⁴¹ A growing number of studies have also demonstrated that the burden of heterogeneous scar is an independent predictor of VT/VF, ICD therapy, and overall mortality.^{42–44} In fact, after accounting for heterogeneous scar burden, LVEF loses most or all of its predictive power.

The mounting body of observational evidence of the utility of scar quantification by MRI in SCD-VT/VF led to the design of the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial.⁴⁵ This randomized study aimed to evaluate the efficacy of ICD therapy in ischemic patients with ≥10% LV scar but whose LVEF did not meet traditional criteria for ICD implant.⁴⁵ Unfortunately, the trial was stopped prematurely, largely for enrollment/funding reasons. This highlights the challenges in bringing promising risk markers to evaluation in randomized trials.

ECG Measures of Depolarization

Finally, we should not forget the original cardiac imaging modality, the ECG. This simple, inexpensive tool may have a role to play in risk stratification for SCD-VT/VF. Abnormalities in depolarization, such as QRS prolongation, may result from myocardial scar. However, depolarization abnormalities may also arise from ventricular dilation or fibrosis, potentially

limiting specificity. QRS duration alone is questionable as a predictor of SCD-VT/VF.^{46,47} Signal-averaged ECG may be more sensitive in detecting late ventricular activation from areas of heterogeneous scar.⁴⁸ However, the positive predictive value of an abnormal signal-averaged ECG has generally been insufficient for risk prediction in patients with ischemic heart disease.⁴⁹ An abnormal signal-averaged ECG was incorporated in the inclusion criteria, along with an LVEF <36%, for the Coronary Artery Bypass Graft (CABG)-PATCH trial, but the combination of these 2 risk factors failed to identify a population that would benefit from ICD therapy.³² Although signal-averaged ECG may have no role in risk stratification of patients undergoing surgical revascularization, its role in other populations remains to be determined.

Fractionation or fragmentation of the QRS complex on ECG may be another specific marker of myocardial scar and consequently may be useful in risk stratification for SCD-VT/VF. In a cohort of 361 ICD recipients with LV dysfunction, a fragmented QRS was a strong predictor of ventricular arrhythmias, whereas QRS duration was a better predictor of overall mortality.⁵⁰ In patients with nonischemic dilated cardiomyopathy, fragmented QRS may be one of the strongest predictors of arrhythmic events.⁵¹ While promising, no standard definition of a fragmented QRS has been established and the inter and intrarater variability has yet to be determined.

Evaluating Cardiac Autonomic Function

The autonomic nervous system plays an integral role in the development of ventricular arrhythmias, particularly in patients with MI or LV dysfunction.⁵² Normal cardiac mechanical and electric function result from a balance of sympathetic and parasympathetic tone. In the setting of cardiac disease, this balance may be disrupted; sympathoexcitation can precipitate VT/VF and parasympathetic activation can be protective. Therefore, measures of autonomic tone have been considered prime targets for risk stratification tools. The main difficulty has been to identify a measure of autonomic function with adequate discrimination for utility in predicting SCD-VT/VF.

Heart rate variability (HRV) has been the most extensively investigated measure of autonomic tone. Loss of vagal tone leads to a decrease in the spontaneous variation in heart rate and was initially described after MI.⁵³ Assessing the utility of HRV for the prediction of SCD-VT/VF is clouded by the numerous potential techniques used to quantify HRV. HRV can be quantified using time domain indices, frequency domain indices, and nonlinear analyses.⁵⁴ Diminished HRV has been associated with both SCD and nonsudden death in MI and in chronic LV dysfunction, independent of LVEF.^{55,56} The poor specificity of HRV to predict SCD-VT/VF may limit its use in risk stratification. The DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) study randomized patients with severely impaired LVEF and abnormal HRV after acute MI to ICD or optimal medical therapy only.³³ The negative results of this trial were, in part, because of high rates of nonsudden death. At present, it is unclear whether measures of HRV can provide adequate refinement of risk of SCD-VT/VF alone.

Heart rate turbulence (HRT) has been evaluated as another noninvasive and reproducible measure of autonomic function. HRT quantifies the short-term variation in heart rate after a

spontaneous ventricular premature beat and is closely linked to baroreceptor sensitivity.^{57,58} However, unlike baroreceptor sensitivity, HRT requires no intervention because it can be measured from ECG recordings alone. HRT has been shown to predict overall mortality, independent of LVEF, after MI.^{56,59} However, in the REFINE study of patients after MI, HRT was also independently predictive of fatal or nonfatal cardiac arrest.¹⁹ Therefore, HRT may be more specific for SCD-VT/VF than HRV.

A recent meta-analysis in patients with nonischemic dilated cardiomyopathy found that none of the evaluated autonomic markers (HRV, HRT, and baroreceptor sensitivity) was predictive of SCD-VT/VF.⁵¹ ECG-based evaluation of autonomic tone may, therefore, not provide an adequate discriminator of risk for SCD-VT/VF. This may be, in part, because of the focus of these techniques on autonomic modulation of the sinus node rather than the disturbed autonomic function of the ventricles, the site of interest for the pathogenesis of SCD-VT/VF.

However, advances in SPECT and PET imaging can allow for visualization of cardiac sympathetic function of the LV.³⁹ Using norepinephrine analogs (such as ¹²³I-*meta*-iodobenzylguanidine and ¹¹C-*meta*-hydroxyephedrine), both PET and SPECT can identify areas of relative sympathetic denervation. In the prospective PARAPET (Prediction of Arrhythmic Events with Positron Emission Tomography) study of patients with ischemic cardiomyopathy receiving an ICD, the amount of viable, but denervated myocardium was independently predictive of the development of VT or arrhythmic death.⁶⁰ Similarly, in the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study of patients with ischemic and nonischemic LV dysfunction, SPECT assessment of global cardiac sympathetic innervation was predictive of both arrhythmic and nonarrhythmic outcomes.⁶¹

Measures of ECG Repolarization

A less well-characterized component of arrhythmogenesis relates to dynamic changes in the cardiac electric system that lead to vulnerability to ventricular arrhythmias. Almost all evaluated measures of such vulnerability are markers of abnormal repolarization on ECG. Several such ECG repolarization measures have been identified.

An abnormal-corrected QT interval on a static ECG has not routinely been independently correlated with mortality or arrhythmic outcomes in patients with MI or with LV dysfunction.⁴⁹ Dynamic changes in the QT interval, in particular QT variability, have been associated with SCD and overall mortality. Yet the discrimination provided by QT variability is insufficient at identifying subgroups at high risk of SCD-VT/VF.⁶²

A more promising measure of dynamic electric substrate is microvolt T-wave alternans (TWA). TWA refers to beat-to-beat changes in repolarization and reflects heterogeneity between cells and cell layers within the myocardium. Increasing heterogeneity leads to increased risk of arrhythmia.⁶³ TWA is a rate-dependent phenomenon that can be assessed by exercise testing or by evaluating spontaneous changes during ambulatory ECG monitoring.⁶⁴ Studies evaluating the utility of TWA in risk stratification have produced mixed results. In a pre-specified substudy of SCD-Heart Failure Trial (SCD-HeFT), TWA was not a predictor of SCD or arrhythmic events in a

chronic, mixed LV dysfunction population.⁶⁵ However, the REFINE study demonstrated that TWA was an independent predictor of fatal and nonfatal cardiac arrest in patients with recent MI, and its discrimination was enhanced in combination with HRT.¹⁹ Similar findings were observed in a secondary analysis of TWA in the randomized Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome (MERLIN)—Thrombolysis in Myocardial Infarction (TIMI) 36 trial in patients with non-ST-segment-elevation acute coronary syndromes.⁶⁶ The ABCD (Alternans Before Cardioverter Defibrillator) trial also showed that TWA was predictive of SCD or ICD discharge, in combination with electrophysiology testing in those with ischemic cardiomyopathy, LVEF <40% and nonsustained VT.⁶⁷ The particular combination of a negative TWA and negative electrophysiology study identified a population at low risk, albeit with a 1-year event rate of 2.3%.

There are several technical aspects that may account for these discrepant results, including timing of testing, a large proportion of intermediate results, concomitant medications, and outcomes used. Nonetheless, the totality of literature supports TWA as predictive of arrhythmic events.^{51,68} Improvements in standardization of methods for assessment of TWA and ease of assessment could increase its penetrance into clinical practice if specific patient populations can be defined in which its predictive value is sufficient.

Provocative Testing and Detection of Subclinical Arrhythmias

Invasive electrophysiology testing in risk stratification for SCD-VT/VF has primarily consisted of programmed ventricular stimulation to assess for inducibility for sustained VT or VF. Electrophysiology testing has a long history in the evaluation of drug therapy for VT, and a positive electrophysiology study was a requirement for ICD implantation in initial practice guidelines. Other potentially important information can be derived at electrophysiology study, such as electroanatomic identification of scar and repolarization measures, but these have not been extensively evaluated in risk stratification.

Although both Multicenter Automatic Defibrillator Implantation Trial (MADIT) and Multicenter Unsustained Tachycardia Trial (MUSTT) incorporated electrophysiology testing, the specific role of the electrophysiology study in risk stratification was evaluated as part of the MUSTT trial.⁶⁹ Patients with ischemic LV dysfunction (LVEF <40%) and nonsustained VT underwent electrophysiology study. Those with inducible VT were randomized to antiarrhythmic/ICD therapy or standard care. The overall trial showed superiority of ICD therapy for inducible patients. However, even in noninducible patients, the rate of cardiac arrest or SCD was 12% at 2 years. Thus, the positive predictive value of electrophysiology testing is high, but the negative predictive value is modest.

The ABCD trial showed that the electrophysiology study may be more useful in combination with noninvasive testing.⁶⁷ The combination of a negative TWA and negative electrophysiology study identified a low-risk group with an event rate of 2.3% at 2 years in a population similar to the MUSTT population.

Thus, electrophysiology testing is likely of most benefit as part of a serial testing strategy. There are also important limitations to electrophysiology testing, including limited ability to predict primary polymorphic VT or VF.

Since the advent of inpatient ECG monitoring, it has been observed that VT/VF is often preceded by nonsustained VT or frequent premature ventricular complexes (PVCs). Frequent PVCs and nonsustained VT are among the earliest established risk factors for SCD-VT/VF after MI.^{27,70} The evidence supporting risk associated with PVCs and nonsustained VT in nonischemic LV dysfunction is weak. A systematic review of risk factors in nonischemic cardiomyopathy failed to identify PVCs and nonsustained VT as independent predictors of prognosis.⁵¹ Yet ambulatory ECG monitoring is attractive as a risk stratification tool because of its ubiquitous availability and ease of interpretation. Numerous trials have evaluated interventions, including drug and ICD therapy, to reduce mortality in patients with frequent PVCs or nonsustained VT after MI or in the presence of LV dysfunction. The majority have shown a reduction in SCD-VT/VF but no impact on overall mortality.^{33,71,72} Consequently, the role of ambulatory monitoring in risk stratification is unclear.

Traditional ambulatory monitoring has numerous potential limitations that may confound its use in risk prediction. The most important of these is sampling error. Stratifying patients on the basis of a relatively short-term ECG recording (usually <7 days) may falsely classify patients and dilute prognostic ability. Advances in ambulatory monitoring now allow for much longer term recordings, with up to 3 years for implantable cardiac monitors (ICMs).⁷³ Contemporary ICMs allow for automated detection of tachy- and bradyarrhythmias with remote transmission capabilities. The large prospective CARISMA trial evaluated the use of ICMs in patients early post-MI with LVEF <40%.³ It provided novel arrhythmia documentation in a contemporary post-MI population, demonstrating a low rate of SCD-VT/VF (6%; >2 years) and an unexpected high incidence of bradyarrhythmias. The utility of ICMs and other emerging monitoring technologies in risk stratification of SCD-VT/VF has yet to be determined but may represent a considerable advance over limited ambulatory ECG recordings.

Summary

Many existing and emerging risk stratification tools have demonstrated good prediction for SCD-VT/VF, and some of the major studies are summarized in Table 2. However, ongoing research is required to determine their clinical utility, impact on outcomes, and cost-effectiveness. It is unlikely that any single measure will have sufficient discrimination to be used in isolation. Rather, combining known measures in a composite score or serial testing needs to be evaluated in this population (Figure). Serial, or stepwise, testing has already shown promise in enhancing risk stratification, particularly after MI.^{67,69,74} Finally, the impact of contemporary revascularization may decrease the proportion of patients with ischemic heart disease, with a relative increase in patients with LV dysfunction from nonischemic processes. The majority of risk stratification tools were developed or validated in ischemic populations. Therefore, validation of these methods in the nonischemic population or the development of a separate risk stratification scheme may be required.⁵¹

Risk Stratification in the General Population

The majority of research and advances in risk stratification have focused on those at highest risk, namely those with MI or LV dysfunction. This, however, ignores the fundamental epidemiology of SCD-VT/VF: the majority of SCD-VT/VF occurs in patients with no known heart disease.^{79–81} Decreasing the population impact of SCD-VT/VF will require improved risk stratification in the general population.

The standard ECG is a potentially attractive tool for large-scale screening of the general population because of its relative low cost and ubiquitous availability. The most comprehensive data on ECG measures and risk of both cardiac death and arrhythmic death come from a series of studies using a Finnish cohort of >10 000 middle-aged subjects followed up for a mean of 30 years.^{82–85} Classification of death was performed retrospectively from available records, which comes with inherent limitations. Nevertheless, in this cohort, QRS prolongation of ≥ 110 ms (prevalence 1.3%; relative risk, 2.14 [1.38–3.33]), intraventricular conduction delay (but not bundle branch block; prevalence, 0.6%; relative risk, 3.11 [1.74–5.54]), and early repolarization of at least 0.2 mV (prevalence, 0.3%; relative risk, 2.92 [1.45–5.89]) were all independent predictors of arrhythmic death.^{82–85} The low prevalence of each of these markers may limit their utility in large-scale screening.

Autopsy and epidemiological data implicate ruptured atherosclerotic plaques (acute coronary syndromes) as a major cause of SCD-VT/VF in the general population.¹⁵ Risk stratification for CAD is well established in clinical practice, yet existing tools were developed to predict overall cardiovascular mortality or the presence of fixed, severe CAD. Most atherosclerotic plaque ruptures occur in nonsevere lesions, and no current risk assessment tools accurately identify patients at risk of ruptured plaque. The ability to identify individuals at risk of plaque rupture would undoubtedly have an impact on prevention of SCD-VT/VF in the general population. Two potential avenues that show promise for better risk prediction in the general population are serum biomarkers and imaging of atherosclerotic plaques.

Serum biomarkers are attractive because of their relatively low cost and generally wide availability. Biomarkers under investigation for risk stratification can broadly be divided into inflammatory markers, free-fatty acids, and hemodynamic markers.⁸⁶ Inflammation plays a central role in the pathogenesis of plaque rupture. C-reactive protein is the most widely studied marker of inflammation although its use in predicting SCD is uncertain. To date, prospective cohort studies have shown mixed results as to whether C-reactive protein levels are independent predictors of SCD.^{87,88} Interleukin-6 is another marker of inflammation. In the large PRIME (Etude PROspective de l'Infarctus du Myocarde) observational study, the highest tertile of interleukin levels was strongly and independently predictive of SCD (estimated odds ratio, >3.0).⁸⁹

Fatty acids are another potential useful biomarker for SCD-VT/VF. The pathophysiologic effects of fatty acids are not completely understood, but subtypes that are protective and that confer increased risk have each been identified. Nonesterified free fatty acids have been associated with higher

Table 2. Selected Important Studies of Risk Stratification for Sudden Cardiac Death-Ventricular Tachycardia/Fibrillation in Patients With Left Ventricular Dysfunction or Myocardial Infarction

Stratification Tool	First Author, Year	Population	n	Outcome	Finding
Identification of anatomic substrate abnormalities					
LV function/LVEF	Bailey et al, 2001 ⁷⁴ (all modalities)	Post acute MI (meta-analysis)	7294	VT/VF or SCD	LVEF <30%–40% is an independent predictor (pooled RR, 4.3); better risk stratification in combination with other parameters such as HRV
Scar assessment	Haugaa et al, 2013 ³⁶ (echo strain imaging)	>40 d after acute MI	569	VT/VF or SCD	Echo strain imaging (mechanical dispersion) independently predictive in patients post MI (HR, 1.7 [1.2, 2.5] per 10 ms increase)
	Van Der Burg et al, 2003 ³⁸ (SPECT)	Survivors of SCD with IschCM	153	VT/VF or death	SPECT excessive scar burden (>1 vascular territory; HR, 2.4 [1.0–5.9] and LVEF ≤30%; HR, 2.0 [1.1–3.5]) only independent predictors
	Roes et al, 2009 ⁴² (MRI)	IschCM receiving ICD	91	Appropriate ICD therapy	MRI transition zone (heterogeneous scar) only independent predictor (HR, 1.5 [1.0–2.2])
	Kwon et al, 2009 ⁷⁵ (MRI)	IschCM with LVEF <45%	349	Death or cardiac transplant	MRI scar assessment independently predictive (HR, 1.02 [1.01–1.03] per 1% scar); LVEF not predictive
Depolarization	Das et al, 2010 ⁵⁰ (ECG)	IschCM and DCM receiving ICD	361	Appropriate ICD therapy	Fragmented QRS by ECG predictor of ICD therapy (HR, 7.6 [3.3–7.4]) but not overall mortality (HR, 1.2 [0.5, 3.0])
Autonomic testing					
Heart rate variability/ baroreceptor sensitivity	La Rovere et al, 1998 ⁵⁶	Recent (<28 d) MI	1284	Cardiac death	Both low HRV (SDNN <70 ms; HR, 3.2 [1.4–7.4]) and BRS (<3.0; HR, 2.8 [1.2–6.2]) were independent predictors; additive prediction when combined with LVEF <35%
Heart rate turbulence	Ghuran et al, 2002 ⁷⁶	Recent (<28 d) MI	1212	VT/VF or SCD	HRT was an independent predictor (turbulence onset HR, 4.1 [1.7–9.8]; turbulence slope HR, 3.5 [1.8–7.1]), in addition to LVEF
	Exner et al, 2007 ¹⁹	Recent (<7 d) MI and LVEF <50%	322	VT/VF arrest or cardiac death	HRT (abnormal onset or slope) an independent predictor when measured 10–14 wk post MI (HR, 2.9 [1.1–7.5]); best prediction with a combination of HRT and TWA
Identification of repolarization abnormalities					
QT dispersion/ variability	Haigney et al, 2004 ⁶²	IschCM and LVEF ≤30%	1232	ICD therapy	The highest quartile of QT variability was an independent predictor (HR, 2.2 [1.4–3.6]), but poor NPV
TWA	Exner et al, 2007 ¹⁹	Recent (<7 d) MI and LVEF <50%	322	VT/VF arrest or cardiac death	Non-negative TWA was an independent predictor when measured 10–14 wk post MI (HR, 2.8 [1.1–7.0]); best prediction with a combination of HRT and TWA
	Gold et al., 2008 ⁶⁵	IschCM and DCM LVEF <35%	490	SCD, VT, or ICD therapy	Non-negative TWA was not an independent predictor (HR, 1.28 [0.7–2.5])
	Chan et al, 2008 ⁷⁷	IschCM and LVEF ≤35%	768	Death and ICD therapy	Non-negative TWA was an independent predictor (at 1 y; HR, 2.2 [1.1–4.3])
Provocative testing/screening for nonsustained arrhythmias					
EP testing	Buxton et al, 2000 ⁷⁸	IschCM, LVEF <40%, and nonsustained VT	1750	VT/VF or SCD	A negative EP study was protective (HR, 0.66 [0.5–0.8]) in comparison to those with positive EP study on no therapy. Event rate with negative EP study still 12% at 2 y
	Costantini et al, 2009 ⁶⁷	IschCM, LVEF <40% and nonsustained VT	566	ICD shock or SCD	A positive EP study was a predictor (HR, 2.4; no confidence interval reported). EP study was more predictive in combination with TWA

The included studies are meant to highlight important literature but do not represent a comprehensive list of studies evaluating tools for risk stratification. BRS indicates baroreceptor sensitivity; DCM, dilated cardiomyopathy; EP, electrophysiology; HR, hazard ratio; HRT, heart rate turbulence; HRV, heart rate variability; ICD, implantable cardioverter defibrillators; IschCM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NPV, negative predictive value; RR, relative risk; SCD, sudden cardiac death; SDNN, standard deviation of normal to normal RR intervals; SPECT, single photon emission computed tomography; TWA, T-wave alternans; and VT/VF, ventricular tachycardia/fibrillation.

risk of SCD. In the Paris Prospective Study I of middle-aged men without known heart disease, nonesterified free fatty acids levels were a moderate independent predictor of SCD.⁹⁰

The most widely studied hemodynamic marker has been B-type natriuretic peptide. B-type natriuretic peptide levels

have been shown to predict SCD and ICD therapy in high-risk populations.⁸⁶ Two large studies in populations without heart disease have identified N-terminal B-type natriuretic peptide as an independent predictor of SCD (relative risk, 1.5–2.5).^{88,91} However, hemodynamic markers are also a significant

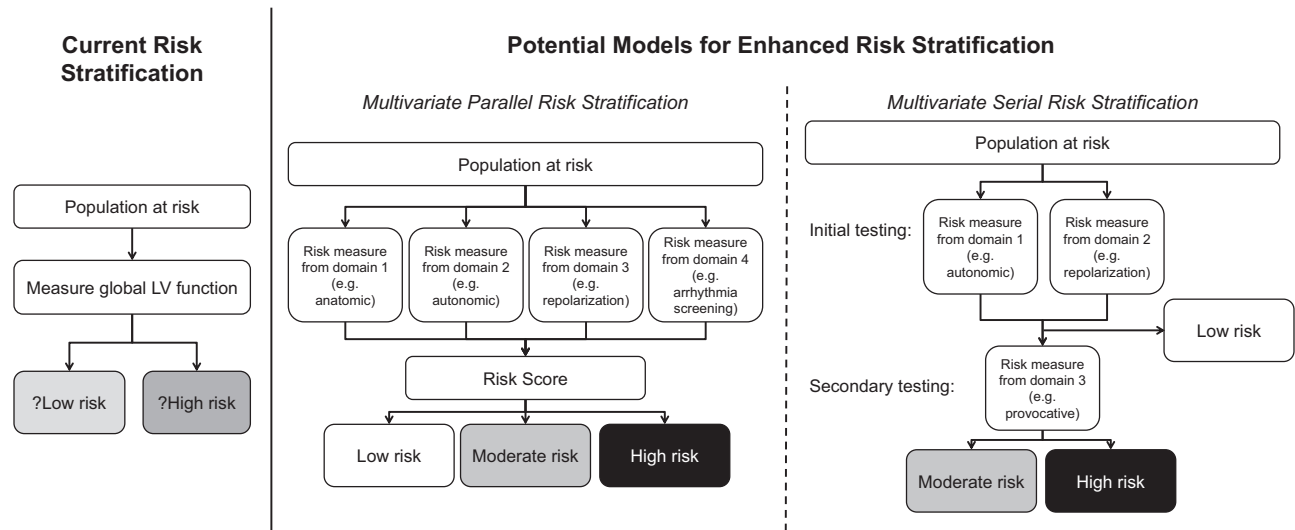


Figure. Models for enhanced risk stratification. LV indicates left ventricular.

predictor of nonsudden cardiac mortality, and their specificity for SCD-VT/VF remains to be elucidated. Biomarkers may be useful in refining risk of SCD-VT/VF in the general population, particularly in those at intermediate or high risk of CAD. Large-scale comprehensive biomarker studies are needed to validate what are typically promising but inconclusive novel reported markers.

Advances in noninvasive cardiac imaging, particularly coronary computed tomography angiography (CCTA), now allow for characterization of atherosclerotic plaque features beyond simple degree of stenosis. In autopsy studies, several features of atherosclerotic plaques have been associated with plaque rupture. Correlates of these features can be accurately identified on CCTA. Two preliminary studies have correlated such adverse plaque features with subsequent risk of acute MI.^{92,93} Further ongoing studies aim to confirm the ability of CCTA to predict acute coronary syndromes in larger populations at risk. Resource implications would obviously limit the widespread use of CCTA for risk stratification in the general population. However, CCTA may be effective in targeted subgroups or as part of a serial testing strategy.

Improving risk stratification of SCD-VT/VF in the general population remains the most pressing and challenging obstacle for the treatment of SCD. Given the causal link between atherosclerotic plaque rupture and SCD-VT/VF in this population, strategies to better identify those at risk of acute coronary syndromes are likely to be the highest yield. Both serum biomarkers and CCTA show considerable promise in this regard.

Risk Stratification in Other Populations

Unique approaches to risk stratification have been developed for specific cardiac phenotypes, notably hypertrophic cardiomyopathy and inherited arrhythmia syndromes.^{94,95} A discussion of risk stratification in these disorders is beyond the scope of this article. Other populations, defined not by a specific cardiac phenotype but rather by demographic or comorbid factors, also warrant discussion to highlight challenges in risk

stratification. Two such populations are those with diabetes mellitus and chronic renal failure.

Diabetes mellitus is present in approximately one fifth of all cases of SCD.⁹⁶ The presence of diabetes mellitus seems to confer an independent increase in risk of SCD, particularly in patients without previous MI.⁹⁷ Diabetes mellitus itself is a risk factor for atherosclerosis and MI, but diabetes mellitus may confer an increased risk of SCD by mechanisms beyond propensity to CAD.

Cardiac autonomic neuropathy seems to be a common finding in patients with diabetes mellitus.^{97,98} Autonomic dysfunction has been associated with an increased risk of overall mortality in diabetes mellitus, but an independent association with SCD has not been established to date.⁹⁹ This mirrors observations on HRV in nondiabetic populations. Diabetes mellitus may increase vulnerability to VT/VF by influencing dynamic myocardial electric substrate. QT interval prolongation is present in a higher proportion of subjects with diabetes mellitus than in controls and is independently associated with overall mortality.¹⁰⁰ Hypoglycemia may be one factor influencing repolarization, including QT prolongation, in diabetes mellitus.⁹⁷ Other measures of repolarization abnormalities, such as TWA, have not been studied in a solely diabetic population to date. Nonetheless, measures of autonomic function and dynamic electric substrate may have particular importance for SCD-VT/VF in the diabetic population.

SCD is also frequent in the chronic renal failure population and particularly prevalent in patients on dialysis.^{101,102} However, defining and classifying SCD in dialysis patients is problematic because the onset of symptoms may be difficult to establish and multiple contributing factors may be present. High overall mortality rates in dialysis patients means risk stratification for SCD-VT/VF must account for competing risks. This is highlighted by the lack of benefit from ICD therapy in dialysis patients who meet traditional LV function criteria for primary prevention ICD implantation.¹⁰³ The use of ICMs in dialysis patients may provide insight into the mechanism of SCD, allowing more accurate estimation of the burden

of SCD-VT/VF versus non-VT/VF SCD. However, no such data are available at present.

The pathophysiology of SCD in dialysis patients undoubtedly has unique features that are not present in other populations. Dialysis results in large swings in electrolyte balance that may influence dynamic electric substrate. This is supported by the increased risk of SCD with increased intervals between dialysis runs.¹⁰⁴ Abnormal parathyroid hormone and bone metabolism in chronic kidney disease may also contribute to the risk of SCD.¹⁰⁵ It is clear that risk stratification in advanced renal failure poses unique challenges. To improve risk stratification for SCD-VT/VF in this population, additional research is required to enhance our understanding of the mechanisms of SCD and its pathophysiology in advanced renal disease.

Future Directions

Risk stratification for SCD-VT/VF remains primitive in clinical practice, yet this need not be so going forward. Many novel risk stratification techniques have been identified that show considerable promise. The majority of these have demonstrated predictive ability, but the clinical utility, impact on outcomes, and cost-effectiveness of these techniques must be evaluated.¹⁰⁶ There are important challenges in risk stratification that must be addressed before meaningful progress can be made.

Contemporary practice is almost solely reliant on LVEF for risk stratification, to the exclusion of other known predictors of risk. More sophisticated models are required to provide accurate estimates of risk to allow physicians and patients to make informed treatment decisions. It is extremely unlikely that any single existing or novel risk marker will have adequate discriminant ability. Multivariable risk modeling has been incorporated into clinical practice for atherosclerosis, bypass surgery, and acute coronary syndromes.^{15,16,107} Relatively simple risk prediction tools have been developed to predict those with reduced LVEF who would not benefit from ICD therapy.^{12,108} Further evaluations of serial testing, particularly strategies of initial testing using a technique with a strong negative predictive value followed by selective testing with a technique with higher positive predictive values, are needed. The ubiquity of electronic medical records and ready access to hand-held computing have eliminated virtually all barriers to rapid, yet accurate risk stratification based on multidimensional input.

There are significant financial, logistic, and regulatory barriers to evaluation of risk stratification techniques for SCD-VT/VF.¹⁰⁹ For many of the important research questions in risk stratification, a conventional randomized control design with treatment and control group will be impractical or impossible. This is particularly true for populations with low event rates for SCD-VT/VF. Randomized controlled trial data also need not be the only standard for assessing the efficacy of risk stratification strategies. Alternate methodologies, such as cluster randomized trials, randomized registries, and prospective cohort studies are more suited to populations with low event rates and complex risk modeling.¹¹⁰

There are exciting advances in medical and device therapy for SCD-VT/VF.^{111,112} Yet defining the roles of these and existing treatments can only take place in the setting of accurate

risk stratification. Improved risk stratification is central to tackling this important public health concern.

Sources of Funding

Dr Deyell is supported by the Michael Smith Foundation for Medical Research and Canadian Institutes of Health Research. Dr Krahn receives support from the Heart and Stroke Foundation of Canada, the Sauder Family and Heart and Stroke Foundation Chair in Cardiology and the Paul Brunes Chair in Heart Rhythm Disorders. Dr Goldberger has received a Path to Improved Risk Stratification conference grant 1R13HL123252-01 from the National Heart, Lung, and Blood Institute.

Disclosures

Dr Goldberger is the Director of the Path to Improved Risk Stratification, NFP, a not-for-profit think tank that has received unrestricted educational grants from Boston Scientific, Medtronic, and St. Jude. He has also received consulting fees from Medtronic and GE Medical. The other authors report no conflicts.

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